

**The Financialization of a Cure:
A Political Economy of Biomedical Innovation, Pricing and
Public Health**



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Abstract

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Sofosbuvir-based medicines, approved in late 2013, offer a long-sought after cure for patients with hepatitis C, a virus that disproportionately affects marginalized populations around the world. But the prices set by its manufacturer at approximately \$90,000 for a three-month regimen intensified a global debate about the pricing of breakthrough medicines. The dominant economic explanations for pricing have centered on ‘risk’, with prices representing the costly and failure-ridden process of drug development, and ‘value’, with higher prices said to reflect improvements in patient health as well as savings from averted downstream medical expenses. These economic explanations are limited, however, by their focus on prices at the point of exchange between drug manufacturers and public health systems.

Instead, I took a historical view, using the case of *sofosbuvir* to trace the political-economic dynamics and organizational relations of power across the innovation process – from early stage science to deployment. Data from documentary sources, semi-structured interviews, databases, and observations at meetings allowed me to build an account of the *sofosbuvir* case. Combining this data with sociological and political economy literatures on the roles of an entrepreneurial state, the rise of financial capital, and the pricing and valuation strategies used by businesses, I argue that *sofosbuvir*’s prices did not represent the tangible costs of innovation or the health value for patients. Rather, the prices were a product of *financialization*: a pattern of accumulation in which growth was pursued through the capitalization and control of intangible hepatitis C assets in financial markets. As part of this pattern, I map the mobilization of speculative capitals behind Pharmasset, a small biotechnology company that emerged from public investments to develop the compound *sofosbuvir*, as well as the extractive logics driving the shareholders of Gilead Sciences, a large publicly traded pharmaceutical company that ultimately acquired Pharmasset and then set the prices for the therapy.

I demonstrate that though an entrepreneurial state shaped the direction of the innovation process towards a curative therapy, the processes of financialization disconnected the distribution of risks and rewards, undermined the sustainability of future innovation, and diminished patient and public health outcomes. I conclude by responding to dominant economic answers on drug pricing in light of the evidence on financialization.

Preface

Declaration of Originality

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except where specifically indicated in the text.

Statement of Length

I attest to the fact that the length of this dissertation does not exceed the 80,000 words limit stated by the Graduate Education Committee at the Department of Sociology. The word count excludes footnotes, and Bibliography.

Acknowledgements

This project is dedicated to my grandfather, who saw me off in India as I began my time at Cambridge, and whose memory and example as a healer will continue to remind me of what's at stake for patients.

To Larry – I am grateful for our many conversations and debates, for your guidance on where to take the project, and for your reading and feedback of my work along the way. As a medical student, I came to Cambridge a relative neophyte on questions of political economy and sociology. I leave with a curiosity made confident and committed to following questions where they lead me. Thank you for challenging me in this direction. Thank you also to my two examiners, Professors Hogarth and Mazzucato, who took the time to thoroughly review my dissertation, engage my ideas, and offer thoughtful comments during my viva. This project and my future research are much better for it.

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Table of Contents

CAST OF KEY ORGANIZATIONS AND FIGURES	4
TIMELINES OF MILESTONES	6
TABLES, FIGURES, BOXES	7
INTRODUCTION	9
CHAPTER 1. SEARCHING FOR ANSWERS ON THE PRICES OF NEW MEDICINES	14
1.1 RISK AND VALUE: THE DOMINANT ECONOMIC ANSWERS ON DRUG PRICING AND BIOMEDICAL INNOVATION	15
1.1.1 RISK AND 'RISKY R&D'	15
1.1.2 VALUE AND 'VALUE-BASED PRICING'	18
1.1.3 THE MONOPOLY-STATE RELATIONSHIP: A PARTIAL ANALYSIS	21
1.1.4 THE LIMITS OF ECONOMIC ANSWERS ON 'RISK' AND 'VALUE' AND THE MONOPOLY-STATE CRITIQUE	23
1.2 CHARTING A DIFFERENT QUESTION	24
1.3 THREE ANALYTIC POSSIBILITIES FROM SOCIOLOGY AND POLITICAL ECONOMY	25
1.3.1 INNOVATION AND AN ENTREPRENEURIAL STATE	26
1.3.2 FINANCE AND FINANCIALIZATION	29
1.3.3 CAPITAL AND CAPITALIZATION AS POWER	35
1.3.4 THE POSSIBILITIES FROM SYNTHESIS: ACTORS, MECHANISMS, AND EVALUATION OF OUTCOMES	39
1.4 REVISITING THE RESEARCH QUESTIONS	41
1.5 A SHADOW EPIDEMIC AND THE SEARCH FOR A CURE: A PRIMER	42
1.5.1 A CHRONIC INFECTIOUS COURSE THROUGH THE LIVER	43
1.5.2 A GLOBAL EPIDEMIC OF SOCIAL DISADVANTAGE	44
1.5.3 SEARCHING FOR THERAPIES	45
CHAPTER 2. RESEARCH DESIGN AND METHODS	48
2.1 CASE STUDY DESIGN	48
2.1.1 WHY A SINGLE CASE STUDY	48
2.1.2 A CASE STUDY OF WHAT? DEFINING THE OBJECT OF STUDY AND ITS PARAMETERS	49
2.1.3 WHY THE INNOVATION PROCESS BEHIND SOFOSBUVIR-BASED TREATMENTS? JUSTIFYING THE SELECTION	54
2.2 DATA SOURCES AND COLLECTION	57
2.2.1 DOCUMENTARY SOURCES	60
2.2.2 SEMI-STRUCTURED INTERVIEWS	62
2.2.3 DATABASES	64
2.2.4 OBSERVATION AT MEETINGS	64
2.3 DATA INTERPRETATION AND ANALYSIS	65
2.4 LIMITATIONS IN RESEARCH DESIGN	68
2.5 SUMMARY OF RESEARCH DESIGN	70
CHAPTER 3. MAKING THE INVISIBLE VISIBLE: THE HANDS OF AN ENTREPRENEURIAL STATE AND A SHADOW EPIDEMIC	71
3.1 DISCOVERING HEPATITIS: FROM THE FRONT LINES OF WAR TO THE NATIONAL INSTITUTES OF HEALTH	75
3.1.1 A HOME FOR VIRAL HEPATITIS RESEARCH: THE EMERGENCE OF THE NATIONAL INSTITUTES OF HEALTH	75
3.1.2 HEART OF A VIRAL HUNT: TRACKING CHRONIC INFECTIOUS HEPATITIS	77
3.1.3 IDENTIFYING THE PATHOGEN: CHIRON, THE CDC, AND THE NIH	81

3.2 OVERCOMING A TECHNOLOGICAL HURDLE: THE REPLICON TOOL	84
3.2.1 GROWING A STUBBORN VIRUS	84
3.2.2 THE NIH EXTRAMURAL PROGRAM AND THE DEVELOPMENT OF THE REPLICON	86
3.2.3 SHARING THE REPLICON WIDELY WITH THE US SMALL BUSINESS PROGRAM (SBIR)	89
3.3 THE TRIPLE HELIX: PUBLIC AND PRIVATE SCIENCE IN THE LAUNCH OF PHARMASSET	91
3.3.1 THE DEVELOPMENT OF NUCLEOSIDE CHEMISTRY AND PHARMASSET AS PUBLIC SCIENCE	92
3.3.2 THE BAYH-DOLE ACT AND THE CONVERSION OF PUBLIC ASSETS	94
3.3.3 PUBLIC RISK-TAKING ON PHARMASSET	97
3.4 FOLLOWING AN ENTREPRENEURIAL STATE: A SUMMARY	99

CHAPTER 4. CHASING THE GOLDEN SNITCH: SPECULATIVE CAPITAL AND SHAREHOLDERS BEHIND SOFOSBUVIR

4.1 SOFOSBUVIR'S DEVELOPMENT AND FINANCIAL MARKETS OF PHARMACEUTICAL ASSETS	104
4.1.1 PHARMASSET'S EARLY ASSETS AND THE ENTRY OF VENTURE CAPITAL	105
4.1.2 A FINANCIAL MARKET OF PHARMACEUTICAL ASSETS: A CORPORATE PARTNERSHIP AND AN IPO	114
4.1.3 SOFOSBUVIR AS A HYBRID BREAKTHROUGH: PUBLIC SCIENCE MEETS PRIVATE ASSET	118
4.1.4 POTENTIAL PATHWAYS FOR PHARMASSET: DURABILITY OR DISPOSABILITY?	122
4.2 LIFE SCIENCE OR SHAREHOLDER SCIENCE? GILEAD'S POSITION IN THE INNOVATION PROCESS	124
4.2.1 GILEAD'S RISE: ACQUIRING AND RECOMBINING INNOVATIONS FOR HIV/AIDS	125
4.2.2 GILEAD'S STRUCTURAL CRISIS: THE SHAREHOLDER GROWTH TREADMILL, PATENT CLIFFS, AND A DRY PIPELINE	127
4.3 CAPITALIZING ON SOFOSBUVIR AND THE HEPATITIS C GOLD RUSH	132
4.3.1 PROJECT HARRY AND THE RELATIONS OF POWER IN PRICING AND VALUATION	133
4.3.2 BETTING ACCUMULATED CAPITAL FOR ACQUISITION AND APPROVAL	139
4.3.3 A SPECULATIVE GOLD RUSH AND THE STRUGGLE FOR HEPATITIS C ASSETS	144
4.4 BUYING BACK OR PAYING FORWARD? FOLLOWING GILEAD'S HEPATITIS C REVENUES	146
4.4.1 THE CANNIBALIZED COMPANY AND GILEAD'S SHARE BUYBACKS	146
4.4.2 STRUCTURING EXECUTIVES TO DISINVEST AND DISTRIBUTE CAPITAL	149
4.4.3 AN OFFSHORE TAX HAVEN FOR SOFOSBUVIR	151
4.5 TAKING STOCK OF SPECULATIVE CAPITAL AND SHAREHOLDERS: A SUMMARY	152

CHAPTER 5. WAITING ON VALUE: GILEAD'S PRICING AND THE CRISES OF THE TRIAGE STATE AND THE PATIENT CLIFF

5.1 SETTING A PRICE FOR A CURE: GILEAD'S \$1,000 A DAY PILL	156
5.1.1 THE BASELINE: A REFERENCE PRICE FROM THE EXISTING STANDARD OF CARE	157
5.1.2 THE POSITION OF POTENTIAL COMPETITORS	159
5.1.3 ESTIMATIONS OF BUYER'S EXPECTATIONS OF PRICE AND 'DIFFERENTIAL VALUE PREMIUM'	161
5.2 THE STATE OF PUBLIC HEALTH OR THE TRIAGE STATE?	164
5.2.1 TURNING TO TRIAGE	165
5.2.2 PUBLIC-PRIVATE POWERS AND THE LIMITS OF VALUE-BASED PRICING	171
5.3 GILEAD'S CONONDRUM: THE LIMITS OF A CURE FOR SHAREHOLDER-DRIVEN GROWTH	179
5.3.1 AN INITIAL HONEYMOON FOR GILEAD	180
5.3.2 A PATIENT CLIFF FOR HEPATITIS C	182
5.3.3 GENERATING GROWTH FOR SHAREHOLDERS: ADVERTISING CAMPAIGNS, CYCLES OF ACQUISITIONS AND BUYBACKS, AND CHRONIC THERAPIES	186
5.4: WAITING ON VALUE: A SUMMARY	199

CHAPTER 6. DIAGNOSING FINANCIALIZATION IN SOFOSBUVIR

6.1 THE ETIOLOGY OF FINANCIALIZATION IN BIOMEDICAL INNOVATION AND DRUG PRICING	202
6.1.1. MOBILIZATION OF SPECULATIVE CAPITALS	204
6.1.2 EXTRACTION DRIVEN BY GILEAD'S SHAREHOLDERS	207
6.1.3 GOVERNANCE OF INTANGIBLE ASSETS AND FINANCIAL CAPITAL BY A MULTI-VALENT STATE	210
6.1.4 SUMMARY OF THE THREE DYNAMICS AND REVISITING EXISTING ANSWERS ON DRUG PRICES	214

6.2 EVALUATING THE OUTCOMES OF THE PROCESS	215
6.2.1 THE DISTRIBUTION OF RISKS AND REWARDS	215
6.2.2 IMPLICATIONS FOR THE DIRECTION AND SUSTAINABILITY OF BIOMEDICAL INNOVATION	217
6.2.3 PATIENT AND PUBLIC HEALTH OUTCOMES	219
6.3 THE LIMITS AND USES OF DOMINANT ECONOMIC ACCOUNTS AS JUSTIFICATIONS	221
6.3.1 RISK AND RISK-MITIGATION	222
6.3.2 VALUE AND VALUE-SHIFTING	224
6.3.3 THE USES OF JUSTIFICATIONS	226
6.3.4 A NOTE ON THE MONOPOLY-STATE RELATIONSHIP	228
6.4 CONTRIBUTIONS, LIMITATIONS, AND QUESTIONS FOR THE FUTURE	229
6.4.1. CONTRIBUTIONS	230
6.4.2 LIMITATIONS AND QUESTIONS FOR THE FUTURE	235
<u>CONCLUSION: BACK TO EXTRACTION AND ONWARDS TO CARE</u>	<u>238</u>
<u>GLOSSARY OF KEY TERMS</u>	<u>240</u>
<u>BIBLIOGRAPHY</u>	<u>242</u>
<u>APPENDIX A: DATA SOURCES</u>	<u>273</u>
DOCUMENTARY SOURCES	273
SEMI-STRUCTURED INTERVIEWS	276
DATABASES	278
OBSERVATION OF PUBLIC MEETINGS	278
<u>APPENDIX B: NIH FUNDING FOR REPLICON AND SOFOSBUVIR DEVELOPMENT</u>	<u>280</u>
REPLICON DEVELOPMENT GRANTS	280
REPLICON COMMERCIALIZATION WITH APATH: NIH SBIR GRANTS	281
NIH GRANTS FOR SCHINAZI-LED NUCLEOSIDE RESEARCH	282
PHARMASSET GRANTS FROM NIH (INCLUDING SBIR)	284
<u>APPENDIX C: ORGANIZATION-LEVEL FINANCES OF PHARMASSET AND GILEAD SCIENCES</u>	<u>286</u>
<u>APPENDIX D: HEALTH ECONOMICS ANALYZES OF SOFOSBUVIR'S VALUE</u>	<u>288</u>
D1. 'COST-EFFECTIVENESS VALUE'	288
D2. 'PUBLIC HEALTH PREVENTION VALUE'	288
D3. A SHORT QALY EXPLAINER	289
D4. LISTING OF HEALTH ECONOMICS STUDIES ANALYZING VALUE OF SOFOSBUVIR-BASED MEDICINES	289
<u>APPENDIX E: KEY DIAGRAMS DEPICTING INNOVATION PROCESS</u>	<u>290</u>

Cast of Key Organizations and Figures

These are key organizations and figures that appear in the dissertation.

Organizations

Public sector organizations

- National Institutes of Health (NIH), US, publicly funded biomedical research organization
- Small Business Innovation and Research Program (SBIR), financing program for small businesses by US government
- Veterans Health Administration (VA), national health care system for US military veterans
- Centers for Disease Control (CDC), US public health agency overseeing research and surveillance over health threats
- Food and Drug Administration (FDA), US regulatory agency which reviews safety and effectiveness of pharmaceutical products, including approval of new medicines
- Securities and Exchanges Commission, US regulatory agency overseeing businesses and financial sector rules
- U.S. Congress, passed key legislation (Bayh-Dole Act) and oversees national finances, such as spending on pharmaceuticals
- Medicare, US health insurance program for elderly over age of 65
- Medicaid, US health insurance program administered by individual states for low-income populations

Business organizations

- Pharmasset, a small biotechnology company that developed *sofosbuvir*
- Gilead Sciences, established biopharmaceutical company
- Apath, a small biotechnology company funded through NIH to support replicon commercialization
- Chiron, a biotechnology company that worked with NIH and CDC to identify hepatitis C virus
- Roche, manufacturer of interferon-based hepatitis C therapies
- Merck, AbbVie, and Bristol Myers Squibb (BMS), leading competitors with Gilead for hepatitis C market

Financial organizations

- MPM Capital, TVM Capital, Burrill and Company: venture capital backers for Pharmasset
- Barclays Capital, investment bank advising Gilead on acquisition
- Morgan Stanley, investment bank advising Pharmasset on acquisition
- Financial market: NASDAQ, stock market for technology companies

Other organizations

- Emory University, the university base for Ray Schinazi, founder of Pharmasset

Key Figures (in order of appearance)

With publicly funded laboratories

- Dr. Harvey Alter, chief, infectious disease and transplant medicine, NIH
- Dr. Ralf Bartenschlager, virologist at Heidelberg University
- Dr. Charlie Rice, virologist at Rockefeller University, founder of Apath

With Pharmasset

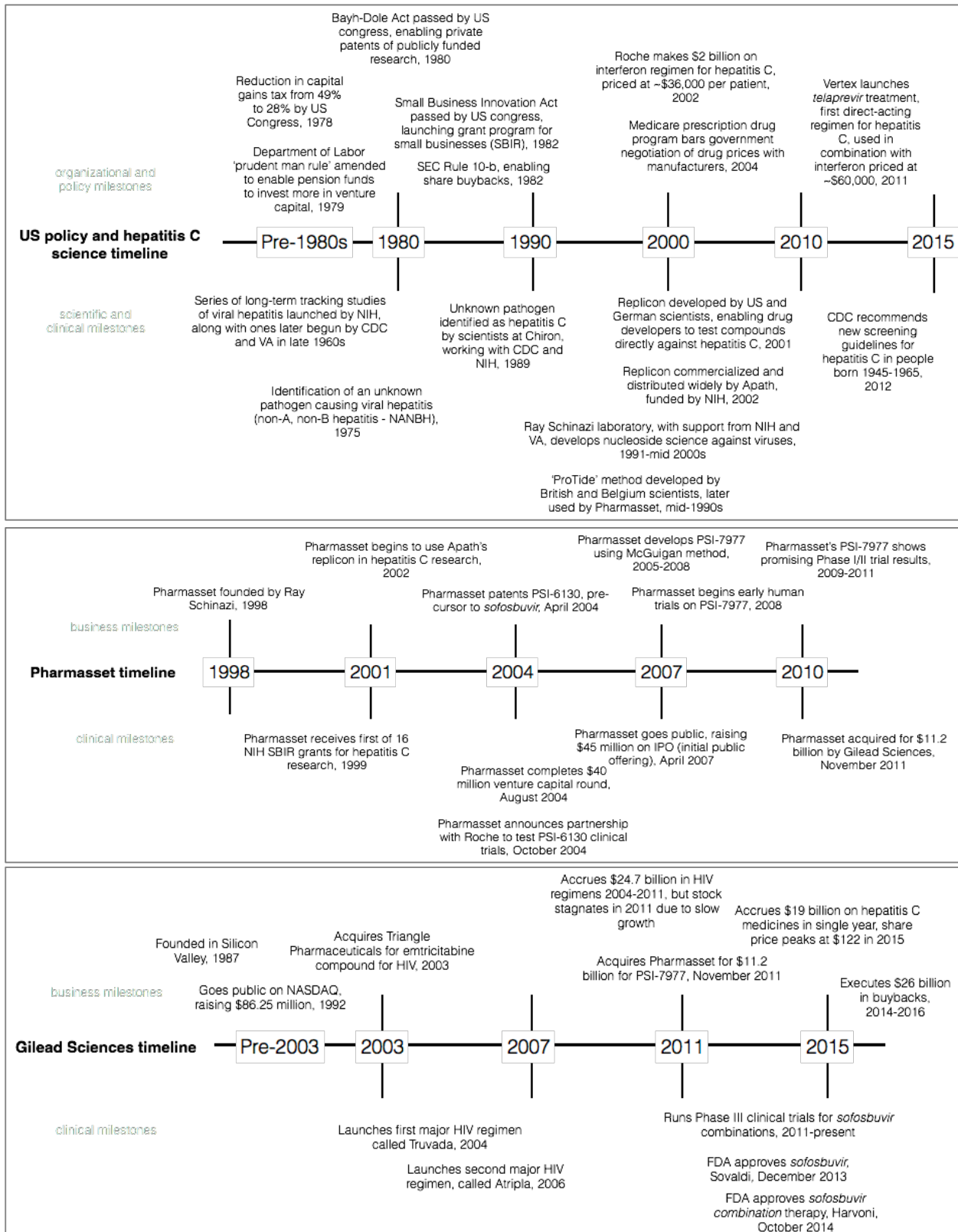
- Dr. Ray Schinazi, founder of Pharmasset, supported by VA and NIH
- Dr. Michael Sofia, lead scientist, Pharmasset and ‘inventor’ of *sofosbuvir*

With Gilead Sciences

- Dr. John McHutchison. head of Liver Disease Research, 2010-2015
- John Martin, CEO from 1996-2016
- John Milligan, Chief Operating Officer until 2016, CEO 2016-present
- Dr. Norbert Bischofberger, Chief Scientific Officer
- Robin Washington, Chief Financial Officer
- Gregg Alton, Executive Vice President

Timelines of Milestones

The first timeline follows broader scientific advances and policy changes relevant to the *sofosbuvir* case, with more specific timelines on Pharmasset and Gilead, the two businesses involved in *sofosbuvir*'s development, covering clinical and business milestones for each.



Tables, Figures, Boxes

Tables

- 1.1 Potential mechanisms of relevance for *sofosbuvir* case
- 1.2 Potential mechanisms for financialization
- 1.3 The shift towards shareholder control
- 1.4 Comparing Assets vs. Commodities
- 1.5 Key dimensions and features of hepatitis C

- 2.1 Parameters of the innovation process
- 2.2 Data sources and collection methods

- 3.1 The entrepreneurial state behind hepatitis C and *sofosbuvir*
- 3.2 Main NIH Institutes involved in hepatitis C research
- 3.3. Regulatory shifts favorable to biotechnology commercialization in 1980s
- 3.4 Timing of NIH SBIR grants and venture capital rounds

- 4.1 Pharmasset's sources of financing, 1999-2011
- 4.2 Venture capital financing of Pharmasset, 1998-2004
- 4.3 Summary of venture capital funds behind Pharmasset
- 4.4 Phase I and Phase II clinical trials for *sofosbuvir* by Pharmasset and NIH
- 4.5: Key figures used in Gilead and Pharmasset capitalization exercises
- 4.6 Main *sofosbuvir*-related clinical trial costs by Pharmasset and Gilead
- 4.7: Gilead's combinations of *sofosbuvir* as part of their 'wave' strategy
- 4.8 Major transactions in hepatitis C between 2011 – 2015
- 4.9 Compensation for Gilead's Top Five Executives, 2014-2016

- 5.1 Key factors in Gilead's pricing strategy
- 5.2 US public health delivery response to *sofosbuvir*-based treatments, 2014-2015
- 5.3: Three strategies to generate shareholder-driven growth
- 5.4 Gilead's share buybacks and average share price after *sofosbuvir* launch
- 5.5: Comparing TDF (old) vs. TAF (new), Gilead's backbone HIV compounds

- 6.1 The three dynamics constituting financialization of *sofosbuvir*
- 6.2 A multi-valent state and the financialization of *sofosbuvir*
- 6.3 R&D costs versus financial returns for Pharmasset and Gilead
- 6.4 Scenarios for coupling prices to production, innovation, and/or public health

Figures

- 2.1: Mapping a triad of multivalent actors and relationship across time
- 2.2 Data collection and analysis across research timeline
- 2.3 Data analysis approach to case study development

- 3.1 The replicon for hepatitis C
- 3.2 Screenshot of Pharmasset website, May 2002

- 4.1 Pricing escalator and expansion of market valuation
- 4.2. Organizational and financial sources of *sofosbuvir* structure
- 4.3 Gilead's share price between August 2006 and December 2010

4.4 Gilead's revenues and capital allocation decisions, 2012-2016* (in billions)

- 5.1 Gilead's initial pricing approaches with existing standard of care
- 5.2 Survey of US payers' anticipation of access at various price points for *sofosbuvir*
- 5.3 Gilead's assessment of potential stakeholder responses to *sofosbuvir*'s pricing
- 5.4 Medicaid requirements for treatment access by liver disease stage as of June, 2015
- 5.5 US hepatitis C epidemic under 'rare disease by 2025' versus 'restricted treatment' scenarios
- 5.6: Historical price escalation from 1986 interferon to 2011 *telaprevir* regimen
- 5.7 Sales of HCV drugs expected to dramatically increase with new patient population
- 5.8 Gilead's lobbying expenses on US federal decision-makers, 2001-2016
- 5.9 Gilead's share price, November 2011 to June 2015
- 5.10 Gilead's hepatitis C (HCV) sales drive quarterly revenue growth
- 5.11: Bloomberg analyst forecast of Gilead's hepatitis C revenue, 2015-2025
- 5.12 Gilead's hepatitis C sales plateau and decline, 2015Q3 – 2016Q4
- 5.13 Gilead's share price, June 2015 to May 2017
- 5.14: Gilead marketing aimed at Baby Boomer patients
- 5.15 Bloomberg analyst perception of Gilead's need for acquisitions
- 5.16 Gilead's capital allocation strategy
- 5.17 Gilead's expected growth from new HIV backbone

Boxes

- 1.1. Clinical trial process in drug development
- 4.1 Gilead by 2011: key primer facts
- 4.2 Cost of capital, the discount rate, and net present value: a brief primer

Introduction

Since their launch in December of 2013, *sofosbuvir*-based medicines¹ have marked a critical breakthrough for patients with hepatitis C infection, offering a cure by eliminating the virus in more than 90% for the patients that take them (Lawitz et al. 2013; Pollack 2013). The virus is a leading infectious killer around the world, disproportionately affecting vulnerable groups such as people who inject drugs, incarcerated populations, and those co-infected with HIV/AIDS (He et al. 2016; Hoofnagle and Sherker 2014; Rosen 2011a). Yet Gilead's launch price – at approximately \$90,000 per three-month treatment course in the US and 'discounted' in other countries – has challenged health system budgets, led to restrictions in treatment access, and ignited a global debate about the pricing of breakthrough medicines (Brennan and Shrank 2014; Walker 2015; Ward and Mermin 2015).

The dominant economic explanations for pricing have centered on 'risk', with prices representing the costly and failure-ridden process of drug development, and 'value', with higher prices said to reflect improvements in patient health as well as savings from averted downstream medical expenses (Chahal et al. 2016; DiMasi et al 2003; Tice et al. 2015).² Critiques of these two rationales have focused on the methodological limits of each while also pointing to the power of an oligopoly-oriented pharmaceutical industry in co-opting the countervailing regulatory function of the state (Light and Warburton 2011; Reinhardt 2015). For reasons I elaborate in chapter 1, the case of hepatitis C suggests that such analyses – both the economics rationales as well as their critiques – have limitations in explaining the prices of *sofosbuvir*.

These economic rationales, as well as the critiques aimed at them, focus on drug prices at the point of exchange between drug manufacturers and governments (via public health systems). Rather than attend to drug prices at a single point of exchange or as an outcome of a single state-business relationship, my dissertation takes a different vantage. I interrogate prices as products of political-economic mechanisms, and bring financial actors into the mix of state and business organizations typically examined. As I describe in chapter 2, I traced the case of *sofosbuvir* – central to contemporary debates on drug pricing – from early stage science to the deployment of the therapy. Informing my investigation were sociological and political

¹ *Sofosbuvir* is the main backbone compound which I trace in this dissertation, and its branded name is Sovaldi. *Sofosbuvir* is used in combination with other secondary compounds to boost its cure rates, which is why I also use the term '*sofosbuvir*-based' treatments at points in the dissertation.

² Often with the support of business interests, these rationales are underpinned by studies using approaches from industrial and health economics (Nik-Khah 2014; Reinhardt 2015; Van Nuys et al. 2015). I detail these approaches in Chapter 1.

economy literatures on the role of the state in innovation, the rise and influence of financial capital, and the control and valuation of assets by businesses (Birch 2016b; Gagnon 2016; Krippner 2005; Lazonick 2015; Mazzucato 2013b; Veblen 1908b). Using documentary sources (including some rarely available internal corporate documents), semi-structured interviews, databases, and observation at meetings, I built an account of the innovation process and pricing strategies behind *sofosbuvir*.

With the evidence from this research, I make two central claims in my dissertation. First, I argue that the prices of *sofosbuvir* do not represent the tangible costs of innovation nor the embodied health experiences of patients. Rather they are a product of *financialization*, a pattern of accumulation in which growth was pursued through the capitalization³ and control of intangible assets in financial markets. I demonstrate that three interrelated sets of dynamics underpinned this pattern of accumulation: mobilization of speculative capitals, shareholder-driven extraction, and governance of intangible assets and financial capital by a multi-valent state. My second claim is that though an entrepreneurial state shaped the direction of the innovation process towards a cure, the processes constituting financialization disconnected the distribution of risks and rewards, undermined the sustainability of future innovation, and diminished the patient and public health outcomes of the therapy. In my final chapter, I juxtapose the dominant economic rationales of risk and value with the collected evidence to illustrate a final point: these economic arguments, serving as justifications for drug prices, are also used to naturalize a given distribution of capital in the innovation process.

In contrast, my research shows that drug pricing in the case of *sofosbuvir* was determined by multiple mechanisms and relations of power that was neither *natural* nor *given*, but rather politically and historically contingent. The U.S. state, for example, through the 1980 Bayh-Dole Act, created the rules by which public science could be converted into private, intangible assets that later became the object of financial speculation. Businesses began to distribute capital to shareholders, rather than reinvest in research and development, due to shifting patterns in corporate governance in the late 20th century. By contrast, explanations that pursue a single culprit or that obscure history can fail to advance current drug pricing debates. For example, in the summer of 2014, the US Senate launched an

³ Most generally, capitalization represents the present value of a future stream of earnings (Nitzan and Bichler 2009). I use the concept of capitalization in this dissertation to show how capitalists value assets not for their present productivity (in terms of profits, for example), but for the future accumulation that control over an asset may bring (for venture capitalists, shareholders, businesses). I suggest that studying the valuation of intangible assets through capitalization is part of illuminating the production of prices for new medicines. I elaborate on capitalization further in chapter 1 before tracing it in the empirical case.

investigation into Gilead's pricing that drew on interviews with senior leadership and over 20,000 pages of internal corporate documents (from emails to board presentations and meeting minutes) detailing the company's strategies (Loftus 2015). At the end of 18 months of bipartisan scrutiny (a rare occurrence in Washington, D.C. these days), the headline of the US Senate Finance Committee's final report flashed across their website: "Wyden-Grassley Sovaldi Investigation Finds Revenue-Driven Pricing Strategy Behind Hepatitis Drug" (United States Senate, Committee on Finance 2015).⁴ The headline fell flat not because the charge made by the committee was not true, but because of how little it (and their 120-page analysis) explained, even with access to a wide array of evidence.

Implicit in this headline, and in critiques made by others, is a sense that business interests are embedded in a social world where other priorities, not just maximizing revenues, should have been considered (Reinhardt 2015). The failure to deliver on the promise of a new biomedical innovation – such as a curative therapy – can be morally troubling because *life itself is at stake*. In 2014, hepatitis C came in as the leading infectious killer in the US, causing more deaths than all other infectious diseases combined, including HIV (Centers for Disease Control 2016a). As a sociologist also training to be a doctor, I am motivated by the ideal of care in biomedicine that underlines the potential – and moral obligation – to use medicine to remedy biological pathologies in a way that may also help restore dignity. Patients with hepatitis C offer testimony to this ideal of care, as they seek treatment as a pathway to both health and freedom from the stigma that so often accompanies their infection (Harris 2009).

Though this ideal reminds us of the underlying motivation for seeking better explanations, the ideal alone is insufficient for finding these answers. Sociological analysis can help ask the right questions, understand the way things are, and how they have unfolded. This insight can then be used to map out the range of fixes that might be necessary for a durable shift towards 'care' that we desire. My hope is that by opening such a space of inquiry through this dissertation, I can contribute towards a much larger effort already underway: to locate the mechanisms, the relations of power, and ultimately the potential sites of intervention in biomedical innovation that can explain and help us address a stark set of challenges.

⁴ Sovaldi is the brand name of *sofosbuvir*.

Plan for the dissertation

This dissertation unfolds in six chapters.⁵ The first chapter details the dominant explanations for drug pricing, poses my two research questions aimed at overcoming the limitations posed by these explanations, and builds an analytical toolkit from sociology and political economy that accompany me in my investigation. The second chapter maps the research design of a single case study and methodology for data collection and analysis used to interrogate the innovation process and pricing behind *sofosbuvir*.

Chapters three through five are the three empirical chapters of the dissertation, chronicling the early stage science all the way into the deployment of the medicines in health systems. In chapter three, I detail the emergence of an entrepreneurial US state in providing the patient capital to unveil the virus as a cause of public health concern and develop the technologies necessary to finding its antidote. This chapter introduces the founding of Pharmasset, the small biotechnology company that emerged from a publicly funded lab to ultimately develop the *sofosbuvir* compound. In chapter four, I document the mobilization of speculative capitals behind Pharmasset as well as the rise of shareholders in shaping the strategies of large, established companies like Gilead Sciences. In tracking the development of *sofosbuvir* across these two companies, I illustrate the function of drug prices along a chain of speculative capital, and map the relations of power at stake between state, business and financial actors. In chapter five, I trace the deployment phase of the innovation process, from Gilead's pricing approach, to the response from the 'health delivery state', and onwards into financial markets that reproduce the dynamics of financialization.

The final chapter uses the findings across these three empirical chapters to synthesize an account of financialization that explain *sofosbuvir*'s prices. I then recount the implications of financialization for the outcomes of the innovation process, including impacts on patient and public health. With this analysis, I return to the economic logics of 'risk' and 'value' used in drug pricing debates to underscore their explanatory limitations considering the evidence I collected. I also suggest, however, that these two logics play a pivotal function in the innovation process by providing justifications aimed at both legitimating drug prices as well as conserving a given distribution of capital. The chapter concludes with a documentation of the contributions and limitations of the study, as well as potential research projects that my findings may provoke.

⁵ I have provided a timeline and cast of key organizations before the table of contents. You will also find a glossary of terms after the main text, as well as appendices with further information that elaborate on my sources of data.

In a brief conclusion, I reflect on the findings of the dissertation within a wider historical context of biomedical innovation, ending by considering what the future may hold. With this background for the plan of the dissertation, I now present the economic debates over the prices of new medicines and my alternative search for explanations.

Chapter 1. Searching for Answers on the Prices of New Medicines

To understand the state of the socially constructed universe at any given time, or its change over time, one must understand the social organization that permits the definers to do their defining. Put a little crudely, it is essential to keep pushing questions about the historically available conceptualizations of reality from the abstract “What?” to the socially concrete “Says who?”
- Peter Berger and Thomas Luckmann, *The Social Construction of Reality* (1966)

Over the past three years, inquiry into the *sofosbuvir* case has been part of a renewed search for answers on prices of breakthrough medicines from across civil society, academia, businesses, and governments. In this chapter, I first map out the prevailing economic answers on drug pricing – focused on ‘risk’ and ‘value’ - and illustrate how they have confounded comprehension into the social mechanisms that produce these pricing outcomes (section 1.1). I also illustrate the limits of focusing on the power of pharmaceutical monopolies in fully explaining the prices of new medicines. Taking up Berger and Luckmann’s (1966) exhortation, I then posit my first descriptive research question (section 1.2) in the pursuit of overcoming the limits of prevailing economic answers on drug pricing.

Next, I trace the three analytical possibilities from sociology and political economy that accompanied me as I investigated the mechanisms behind the prices of *sofosbuvir* (section 1.3). This scholarship pointed me towards dissecting relations of power at stake between multivalent⁶ state, business, and financial actors in the innovation process. Upon reviewing these bodies of literature, I revisit my research inquiry and pose a second question, which aims to complement the initial *descriptive* question with an inquiry that seeks to critically *evaluate* the outcomes of the innovation process behind *sofosbuvir* (section 1.4). Finally, I end the chapter by providing a brief primer into the clinical, public health, and drug development features of hepatitis C, thereby enabling an informed entry into complex political-economic *and* scientific terrains (section 1.5).

⁶ By multivalent, I hold each of these set of actors to be composed of multiple organizations and actors with differentiated interests and involved in varied relations of power with other actors. For example, within the ‘state’, I examine public sector organizations that fund innovation but also regulatory organs and health delivery systems that are involved with biomedical innovation; within ‘business’ I investigate small biotechnology companies versus larger, established companies; within ‘finance’, I look at different forms of financial capitalists, from venture capital to institutional shareholders. I elaborate on this perspective in my research design and methodology chapter (chapter two).

1.1 Risk and Value: The Dominant Economic Answers on Drug Pricing and Biomedical Innovation

The dominant economic answers for the price of new medicines center on two logics, both of which are inextricably linked to the patent-protected model of biomedical innovation. The first is the ‘risk’ logic, in which patent protected pricing power is presented as necessary to fund costly and failure-ridden research and development (DiMasi et al. 2016). The second is the ‘value’ logic, in which higher prices reflect improved patient health outcomes and averted downstream medical expenses (Gregson et al. 2005). These rationales are buttressed through studies from industrial and health economics and also constitute the primary discourse in which policy debates over drug development and pricing occur (DiMasi et al. 2016; Institute for Clinical and Review 2015). In the contested arena of drug pricing and development, critics challenge these justifications, responding to both logics with claims of methodological errors, evidentiary omission, as well as an interrogation of the deleterious influence of the monopoly power of pharmaceutical companies over the state.

In this section, I detail the justifications and evidence behind each economic logic and explicate the critiques of both. I also explore the political economy of the state-monopoly relationship, typically posed as a counter to economic answers on drug prices. I conclude, however, by arguing that the current debate – both defenses of ‘risk’ and ‘value’ as well as their critiques – fall short of understanding the wider social and political-economic dynamics behind the prices of new medicines.

1.1.1 Risk and ‘risky R&D’

Before sharing the specifics of Gilead’s pricing strategy, the company’s COO John Milligan offered a general claim in October of 2014 to an audience of policy makers in Washington DC that would frame the rest of his remarks. “We do all of this at enormous risk,” Milligan asserted, thereby underlining the need for Gilead to receive a reward in exchange for bringing a new curative therapy to market (Brookings Institution, 2014). Milligan’s claim offers partial insight into the ‘risk’ logic used in prevailing accounts of drug development and pricing.

Manufacturers like Gilead Sciences price new medicines with the anticipation that there will be little or no competition due to publicly-granted patents over the intellectual property for a newly approved compound (Scherer 2001; 2004). This patent-centered configuration has long been argued by the pharmaceutical industry to be necessary to finance research and development into medicines (DiMasi et al. 2003; Harper 2010; Love 2014b). From this vantage, patents are

understood to facilitate scientific development, in which inventions receive monopoly rights for a specific period of time (20 years from the time of the invention) only after which the public can gain full access (i.e. generic licensing) to the knowledge protected by the patent (Grabowski 2002). As Biagioli (2006) has pointed out, patents technically govern a legal exchange between ‘consumers’ and ‘investors’ of patent protected products, with these transactions conceptualized in the law as a ‘bargain’ or ‘fair exchange’: investors’ right to recuperate costs of research and development in exchange for customers’ access to the inventor’s product.

Under this model, the assumption is that patent-protected prices (and the resulting revenue) are paying for the costs of research development. The industry, funding and leaning on a series of economic studies since the early 1990s, has sought to demonstrate that costs of research and development are high and growing, thereby justifying their pricing strategies as a necessary vehicle for further innovation (PhRMA 2015). Most prominently, a group of economists at the Tufts Center for Drug Development has published models showing that the cost of developing a drug has increased from \$231 million in 1991, to \$802 million in 2003, and up to \$2.6 billion in 2014 (DiMasi et al. 1991; 2003; 2016). These numbers have been developed on the basis of what they argue are several inescapable features of drug development. One feature is the lengthy period over which investment must be made, with an average calculated to be 11 years to approve a new medicine in the DiMasi studies (DiMasi et al. 2016). A second is the high level of risk, with revenues from patent protected prices paying not only for successes but the thousands of compounds that fail to make it to approval (DiMasi et al. 2016). The third central feature is the industry’s ‘cost of capital’, or ‘opportunity cost’ of investment (estimated to be 10.5% in the DiMasi studies), as this capital could otherwise go to sectors with fewer risks and shorter product development cycles, such as information technology (Damodaran 2017; DiMasi et al. 2016) .

This knowledge has been used to posit a particular ‘cost-plus’ version of pricing, which we can formally represent here (Gregson et al. 2005):

$$P = C + I,$$

where C = cost of research and development⁷, and I = profit

⁷ Additional costs also include manufacturing and operations, though these are generally minimal for most therapeutics. For the purposes of demonstrating the point about risk, I present C as the cost of research and development in this equation.

Critiques of this ‘risk’ argument have typically focused on the methodological and evidentiary limits of these studies. These critiques demonstrate alternative methods that show the extent to which the industry ‘inflates’ their figures and point to the fact that the data in the Tufts studies are provided by the industry and shrouded from public scrutiny (Adams and Brantner 2006; Light and Warburton 2011; Love 2003; Pflumm 2011). For example, in analysing the 2004 Tufts study which reported a \$802 million figure per drug developed, Light and Warburton (2011) used a different set of assumptions and data set to estimate a much lower figure of \$180-\$231 million per-approved compound. Multiple studies have shown that companies spend much more money on marketing than research and development (Swanson 2015; Angell 2004; Gagnon and Lexchin 2008). For example, a study by Gagnon and Lexchin (2008) calculated that the industry spent \$58 billion on promotional activities in 2004 alone, more than double their total research and development spending for the year.

Yet this debate suffers from more than just an inconsistent or non-transparent evidentiary base – the lack of a definition of risk or an account of how the organization of drug development has shifted, particularly in the last two decades, leaves these ‘risk’ findings open to multiple interpretations. First, in the Tufts studies, for example, all units of research and development dollars that are ‘risked’ are quantitatively treated the same in dollars; yet not all dollars spent on research and development are the same. Spending on minor improvements, or late-stage trials carry distinctly different technical ‘risks’ than investments in uncertain early-stage research (Pisano 2006). Indeed, it is not just the ‘amount’ spent on research and development, but *how* and *when* that also needs to be considered in any interpretations.

Second, this debate does not account for the shifting industrial structure in biotechnology and pharmaceuticals, assuming most compounds to be ‘self-originating’ within single firms (Avorn 2015). Yet over the past thirty years in which DiMasi’s studies have been at the center of the debate, the industry has shifted towards a structure in which many compounds travel through public-sector and small biotechnology companies while changing hands multiple times (Pisano 2006). This debate has remained silent on the question of how to ‘count’ the costs of these transactions (i.e. acquisitions) and the contingent speculative dynamics of financial markets (i.e. ‘asset bubbles’ and ‘gold rushes’ in particular therapeutic areas) in which drug development now occurs.

Finally, even with the ‘real data’ on drug development costs, these numbers would still leave significant space for interpretation about the meaning of the data and rationale for drug

prices. For example, the economist Dean Baker ‘flipped the script’ on the release of DiMasi’s \$2.6 billion estimate in 2014, using it to claim that the rising costs indicated an increasingly inefficient monopoly-based industry, thereby challenging the very justification for patents that the DiMasi studies aimed to legitimate (Baker 2014). Another study by a group of biotechnology investors into falling productivity – measured in terms of rising costs of research and development per drug approval – posited four distinct reasons for why this could be (Scannell et al. 2012).⁸ Any of their four interpretations of falling productivity would have different implications for drug prices. In sum, the analysis over whether prices reflect the costs of research and development leaves us with more questions than answers. What about the other main logic advanced in the dominant economic account of drug pricing?

1.1.2 Value and ‘value-based pricing’

The second orientation towards drug pricing has centered on the notion that health system leaders want ‘value for money’, with value defined as better health outcomes as well as reduced downstream medical expenses from averting disease progression (the value of prevention). Higher prices, in this calculation, reflect the potential value of patient and public health improvements (Gregson et al. 2005). Because individuals cannot pay for this value – as the price of new medicines tend to be multiples above the median wages of individuals in most countries – this responsibility to value new medicines falls to health system leaders, who make determinations over how they can generate the most health improvement in their populations with the dollars they have (Iyengar et al. 2016; Reinhardt 2015). From the perspective of the manufacturer, pricing strategies should reflect the value to health systems via setting a ‘value-based price’. As industry consultants Gregson et al (2005:121) puts it, “in contrast to historic approaches for which the company perspective was dominant and product prices tended to be on a ‘cost plus margin’ basis, pricing theory and practice now recognize that the needs and perspectives of the customers must be the starting point for pricing-strategy development.” In this reflection, Gregson points to the shift from the risk-dominant logic for pricing, and posits health systems as ‘customers’.

⁸ These four hypotheses by Scannell et al (2012) were 1) the notion that earlier drug development already took on the ‘low hanging fruit’, with newer efforts now taking on more challenging scientific and technical problems, thereby being more costly (they call it the ‘Better than the Beatles’ problem); 2) the ‘cautious regulator’ problem, in which a swing towards more regulation may be leading to higher hurdles for companies, 3) the possibility that managers waste money by ‘throwing money’ at R&D, and 4) an over-reliance on technological high throughput screening methods for potential therapeutics (‘brute-force’ bias).

The assessment of ‘value’ has been developed using a number of quantification approaches, with health systems and public health officials (the ‘customers’) using ‘cost-effectiveness analysis’ (CEA) and manufacturers increasingly recruiting ‘pharmacoeconomics’ teams to build an evidence base for their pricing (Gregson et al. 2005; Maldonado Castañeda 2016). These approaches typically attempt to quantify two ‘values’: the value of the new therapy in comparison to a reference product or treatment (such as existing standard of care) as well as the value of prevention (from averted downstream medical expenses).⁹

In the first valuation, the difference in the costs of the new therapy and the reference therapy are divided by the difference in the health improvements of the new versus reference therapies (Clement et al. 2009). While the ‘costs’ are typically the prices of a complete treatment regimen, the health improvements are quantified by using ‘quality-adjusted life year’ measurements (QALYs). Developed and used widely in health economics and public health, QALYs measure patients’ ratings of their health statuses under different conditions (i.e. for example, having progressive liver disease might be .7 on a scale of 1, with 1 equalling full health) (Weinstein et al. 2009). Health benefit can thus be measured using the differences in QALYs created by different medicines (Weinstein et al. 2009). This ‘cost per QALY’ ratio is then compared against the ‘value threshold’ that a health system sets, which is the additional amount that a health system is ‘willing to pay’ for an additional QALY for patients. If a medicine is below the threshold, then it has a ‘value price’ for which health systems would ideally be willing to reimburse a manufacturer (Reinhardt 2015). The National Health Services (NHS) in the UK, for example, typically pays for medicines that are within £20,000 to £30,000 per QALY (Claxton et al. 2008). This methodology is used widely across Europe via ‘health technology assessment’ (HTA) bodies, such as National Institutes for Clinical Excellence (NICE) in the NHS system; payers in the US, even with less direct government pricing regulation, are beginning to incorporate such studies into their deliberations over how much to pay for a medicine (Bach and Pearson 2015; Institute for Clinical and Review 2015; Pearson and Rawlins 2005).

With medicines that have population health level implications, such as the *sofosbuvir*-based treatments, the valuation also takes the second step: calculating the total value of downstream medical expenses averted at a health systems-level through early diagnosis and treatment in comparison to the status quo (with the existing standard of care) (Dumit 2012b;

⁹ See Appendix D for more on this valuation approach, as well as the studies that analyzed *sofosbuvir*.

Gregson et al. 2005; Maldonado Castañeda 2016). For example, in the case of hepatitis C, pharmacoeconomic studies have shown that health systems could save billions in averted liver transplants and hospitalizations by treating patients early, even at Gilead's launch price point (Chahal et al. 2016; Van Nuys et al. 2015). Taken together, these two valuation practices aim to advance a second kind of pricing strategy, represented as such (Gregson et al. 2005):

$$\text{Price} = \text{Value} = R \pm D,$$

with R = reference product price and D = differential value¹⁰

This pricing strategy is still inextricably linked to the patent-based system, as companies make these estimations with the anticipation of only limited, if any, competition because of intellectual property protections. But the value based pricing strategy requires a different kind of calculation for manufacturers. Gregson et al (2005:122) describe this change: "In essence, the fundamental pricing question has shifted from 'what price do we need to charge to cover our costs and make a good return?' to 'Given market perceptions of value, which products can we profitably produce?'" In this way, manufacturers conceive of different health systems – typically national governments – as a 'market' to which they are calibrating their pricing, even though companies with new medicines may face little competition.¹¹

Criticisms of this value-based pricing logic have tended to come in two varieties. The first one is the methodological challenge of objectively measuring health improvements in monetary terms (i.e. costs per QALY) (Knapp and Mangalore 2011; Nord et al. 2009). QALY measures, for example, can suffer from variations based on differences in patient populations and the extent to which patients' valuation of dimensions such as reduced social stigma can be reflected in studies (Nord et al. 2009). Furthermore, the financial value imputed to each quality adjusted life year can appear arbitrary, with a country's GDP serving as the closest proxy – in the UK, QALYs are valued at 20,000 - 30,000 GBP, whereas US health systems typically use values ranging from \$50,000 to

¹⁰ This differential value is the company's estimation of what 'the market' perceives to be the value of the company's product in comparison to an existing standard of care or other reference product.

¹¹ In making this shift, companies are increasingly appropriating valuation logics from governments that the industry had generally resisted as pricing regulation in an earlier era. Government health systems around the world have indicated that 'paying for value' is a key priority in the face of aging populations, rising health care costs, and limited budgets. For example, a centerpiece of the Affordable Care Act ('Obamacare'), in addition to expanding health insurance, has been paying for 'value-based health care' in which doctors and hospitals are reimbursed less for services ('fee for service') and more for actual improvements in health outcomes (Obama 2016). Companies are now increasingly using this value logic to legitimate prices to government health systems (Reinhardt 2016).

\$150,000 (Neumann and Cohen 2014). The second criticism is that when deciding over a new medicine, value-based evaluations in health economics compare single interventions against each other, leaving wider budgetary concerns un-addressed (Reinhardt 2015). For example, in the case of hepatitis C, new *sofosbuvir*-based medicines were compared against the existing standard of care at the time, interferon-based regimens, which were already priced at more than \$80,000 per patient. *Sofosbuvir*-based medicines offered a far greater health value than older interferon treatments; this quality also meant that more patients demanded the treatment. Yet by using the older reference price as the baseline with which to value *sofosbuvir*, health systems faced a major quandary: more patients could benefit from a treatment at prices that threatened to displace spending in other areas of health and social concern (Rosenthal 2014; Rosenthal and Graham 2016).¹²

These critiques of value-based pricing, however, leave a larger array of questions unaddressed. A narrow focus on the exchange between a manufacturer and buyers – and the determination of value at this exchange – renders the potential *flow* of value, from value creation to value extraction, invisible (Mazzucato 2016; Reinhardt 2016). What are the resources that generate ‘value’? Where do such prices come from (i.e. why was the reference price for *sofosbuvir* already \$80,000)? Where does the value that is exchanged in such transactions go? How might its destination be part of evaluating the innovation process? Such questions are immaterial in this constricted conception of value. Both the ‘risk’ and ‘value’ logics as the prevailing economic answers on drug pricing for new medicines leave us with the opportunity to search anew for answers.

1.1.3 The monopoly-state relationship: a partial analysis

In critiquing these economic answers, one common set of analyzes is based on scrutinizing the ‘monopoly-state’ relationship (Adams and Brock 2004; Angell 2004; Baker 2014; Goozner 2005).¹³ In this lens, popularized through works such as Marcia Angell’s (2004) *The Truth about the Drug Companies*, pharmaceutical companies – granted monopolies over intellectual property by the state in order to take on risky research and development efforts – have in turn co-

¹² I elaborate on these pitfalls in chapters 5 and 6 at greater length.

¹³ By ‘monopoly’ I refer to the fact that companies are granted patent protections for each of their specific therapies, effectively giving companies monopolies in therapeutic areas where they own the only or best-in-class treatment. Some therapeutic areas can resemble oligopolies, with a small number of competitors producing similar patent protected medicines.

opted the state to charge high prices while failing to produce consistent innovation. Through political lobbying and regulatory influence, the industry has been able to bias legislation and rule-making in its favor to protect and broaden their property protections, diminish competition, and limit measures to increase the countervailing power of government health delivery systems with regards to drug pricing (Adams and Brock 2004; Baker 2014). Furthermore, in this state-monopoly relationship, pharmaceutical companies not only co-opt the health delivery state, but as illuminated in Merrill Goozner's (2005) *The \$800 Million Pill*, appropriate government-funded science by gaining property rights over technologies developed with taxpayer money. The state here is thus seen as a payer of two kinds of public goods - scientific research as well as health care (in the US, for vulnerable populations such as the elderly and poor).

This political economy analysis provides a partial advance into our understanding of drug prices by illuminating the influences of monopolies. However, this critique falls short on three major counts. First, the analysis does not examine the ways in which research and development is influenced by new patterns of finance. For example, in examining the financing of biomedical innovation across the product development process, only the capital allocation and pricing decisions of large pharmaceutical companies are under scrutiny. As I raised earlier, shifting models of biotechnology development, such as venture-backed companies, present new financial dynamics to consider in debates over drug pricing and innovation (Lazonick and Tulum 2011). Second, this analysis holds a narrow view of the state, producing public goods such as basic science and paying for medicines, while struggling to exercise countervailing power in the face of powerful pharmaceutical companies. Yet as I will illustrate later in the chapter, other scholars have pointed to the multiple and shifting roles the state plays in the innovation process beyond the provision of public goods, such as making entrepreneurial investments that proactively shape and create markets (Mazzucato 2013b).

Finally, a deeper interrogation and potential critique of the prevailing 'risk' and 'value' arguments are not possible without a broader analysis that brings in financial capital as well as the state in its multiple forms. Without such analysis, evidence of diminishing investments in research and development (especially in a context of high drug prices), is explained as pharmaceutical companies abusing the patent protections that the 'risk' argument legitimates (Angell 2004). The value answer can be explained as another ploy to maximize profits for manufacturers (Bach 2015; Reinhardt 2015). The causal story in each critique is reduced to a single actor's power and the limited countervailing response of the state; absent is a historical

consideration of the wider political-economic contexts within which business monopolies and state actors have evolved.

1.1.4 The limits of economic answers on 'risk' and 'value' and the monopoly-state critique

The dominant economic answers of 'risk' and 'value' as well as the monopoly-state critique share a blindspot: they largely abstract drug development and pricing away from the historical and political-economic contexts in which they occur. Before I pivot to charting a different research direction through the case of *sofosbuvir*-based medicines, I briefly summarize the three consequences of this blind spot as a way of defining an alternative agenda for inquiry.

First, existing answers rely on static, atomistic units of 'risk', 'value', and 'monopoly' which reduce prices to a single interaction between business and buyer, rather than *dynamic*, *differentiated* concepts that can be used to interrogate an innovation process. As I described above, realities and perceptions of risk change along the innovation process, and actors respond to and manage this risk in different ways. Value is not simply exchanged in one transaction - it has sources of creation, flows, and directions underpinning these flows (i.e. value creation to value extraction). The patents that grant companies 'monopoly' can also shift in purpose across an innovation process as ownership claims change hands between small and large companies (i.e. patents may be used to raise venture capital for small companies, patents may later become a potential asset for acquisition by a larger company). Thus, rather than taking static units of 'risk', 'value' and 'monopoly' as a given, I aimed to dissect them across an unfolding innovation process.

Second, both economic answers as well as the critique of the state-monopoly relationship attempt to place a single actor 'on trial' for the benefits of a given system of drug pricing and development, rather than search for mechanisms that includes multiple organizations and relationships. The focus has been primarily on the contributions or abuses of established large pharmaceutical companies in pursuing research and development, or on the ability (or inability) of government to regulate prices or pay for new medicines. In attempting to find a single culprit, this vantage tends to present state and business as monoliths, and ignores the influence of financial actors in the innovation process. By bringing in an analysis of finance, as well as considering multiple organizational actors, I aimed to be open to a larger array of mechanisms and relations between actors that shape drug pricing and development.

Third, existing economic answers and their methodological critiques tend to reproduce the discourses of 'risk' and 'value' at play in debates over drug pricing. Rather, I aimed to situate these discourses within historical and material relations of power to understand their changing

role and sway within debates over drug development and pricing.¹⁴ Such a descriptive endeavor may then help illuminate more precisely the functions of existing ‘risk’ and ‘value’ arguments in the innovation process (i.e. what they obscure, conserve, enable), locate the relations of power that underpin these functions, and more deeply appraise the limits of these economic answers.

Thus, I sought to pursue a direction of research – both the right questions as well as accompanying analytical tools from sociology and political economy – that allowed me to move from *static units to analytical concepts of an innovation process*, from *the logic of the trial* to a *descriptive search for mechanisms between multiple organizational actors*, and from *discourses of debate to relations of power*. By attempting to make each of these pivots in my research, I aimed to develop a more rigorous understanding of the forces, relationships, and actors influencing drug pricing.

1.2 Charting a different question

Rather than ask ‘are the prices of new medicines justified?’ – which is where prevailing economic accounts and their critiques place their attention – I sought to ask a question that did not have a yes/no answer nor was a test of a single variable or relationship. My investigation instead was oriented around a ‘how’ question¹⁵:

How do the organizational and political-economic dynamics in an unfolding innovation process explain the prices of sofosbuvir-based medicines for hepatitis C?

In asking a how question, I aimed to take a wide frame to my investigation, and thereby arrive at a valid representation of the innovation process and its pricing outcomes. My question specifically contained three elements that ensured that I departed from the common pitfalls of answers cited earlier. First, I wanted to be open to the roles that *multiple organizational actors* potentially played, beyond large pharmaceutical companies and the health delivery state (i.e.

¹⁴ For example, I attempt to situate the more recent and public shift by the industry to use the ‘value’ argument within new political-economic models for drug development driven by financialization. By situating the discourses within their historical and material contexts, I could shed light more precisely into what gets obscured in current uses of the ‘value’ discourse. I return to this analysis in Chapter 6.

¹⁵ Based on my sociological vantage and review of the literature, my research question assumed the domain of analysis to be within organizational and political-economic mechanisms – rather than other potential domains, such as psychosocial explanations of the financial desires of corporate executives, or cultural anthropological takes on the way different actors in society value innovation and biomedicine. Given the large-scale structural and social dynamics at play in biomedical innovation involving state, business, and financial actors, I found this to be the most robust and yet focused domain within which to look for answers.

small biotechnology companies and financial actors). Second, I embedded my organizational analysis in *political-economic dynamics*, thereby aiming to study the relations of power between these actors within a historical context. Third, I took the lens of an *unfolding innovation process* in order to interrogate how the relations between these actors, as well as the concepts of ‘risk’, ‘value’, and ‘monopoly’, may shift during the trajectory that drug development takes. I further elaborate the implications of this orientation in the discussion of my research design and methods in the following chapter.¹⁶

1.3 Three Analytic Possibilities from Sociology and Political Economy

Making such an interrogation requires entering and navigating the complex and shifting terrain on which biomedical innovation occurs. But I am far from the first to attempt this tall order. To answer my question, I was accompanied by previous works from within political economy and sociology traditions that have examined the organizational and political-economic dynamics shaping biomedical innovation. From my reading of this literature, three threads of inquiry provided mechanisms that I hypothesized could account for the innovation process and prices of *sofosbuvir*-based medicines.

Each thread emphasized the role and influence of a different set of actors and in the innovation and pricing process. The first thread interrogates innovation in processual terms as a collective and cumulative endeavour, featuring an *entrepreneurial state* playing a critical role in confronting the risk and uncertainty involved with developing therapeutic breakthroughs. The second thread, linked to the first, maps the relationships between finance and the innovation process, and through the concept of *financialization*, identifies the rise of new patterns of accumulation in shaping the anatomy as well as directional and distributive outcomes of biomedical innovation. Finally, a third thread traces the relations of power between business organizations and other social actors (such as competing businesses, the state, financial sector) by elucidating the *capitalization*¹⁷ and control by businesses of a community’s assets to generate and amass capital in the economy. Each thread provided partial and potential explanations which I could explore in the *sofosbuvir* case (see Table 1.1). I now describe each in turn.

¹⁶ I define and justify the parameters of the question and case study later in the research design and methodology chapter (Chapter 2).

¹⁷ By capitalization, I refer to valuation of anticipated future earnings streams from the ownership and control over (intangible and tangible) assets. I further define capitalization in the context of my dissertation when I review Veblen’s development of the concept later in the chapter.

Table 1.1 Potential mechanisms of relevance for *sofosbuvir* case

Analytic thread	Potential organizational and political-economic mechanisms
Entrepreneurial state	<ul style="list-style-type: none">- The state confronts the radical uncertainty involved with innovation through patient, risk-taking capital.- State investments can overcome technological frontiers, shape the directions of the innovation process, and 'dynamise in' private capital – rather than 'fix markets' or 'crowd out' investment.- State policies shape the relationship between public and private actors, such as by governing the rules by which entrepreneurial public investments can be used.
Finance and financialization	<ul style="list-style-type: none">- Patterns of accumulation have shifted away from profits accruing from trade and commodity production and towards financial channels.- Speculative financial markets, rise of shareholder power, and state actions are potential pathways that have enabled this shift towards financialization in the economy.
Capital and capitalization as power	<ul style="list-style-type: none">- Capital is the quantified ownership and control over grouping of intangible and tangible assets from a wider community- Capitalists pursue an accumulatory advantage versus other capitalists, thereby valuing assets based on their capability to generate <i>differential</i> growth through anticipated streams of earnings in the future. The calculation of these future streams of earnings in terms of present value is called capitalization.- Capitalization processes are sites at which multiple social relations of power can be dissected.

1.3.1 Innovation and an entrepreneurial state

When *sofosbuvir* was approved for use in late 2013, the medicine replaced an array of older medicines for hepatitis C that had proven noxious for many patients but had until then represented their only hope (Pollack 2013). If we understand one part of any definition of innovation to be the generation of a better-quality product, *sofosbuvir*, unlike many 'me-too' medicines with minor or no therapeutic advance, appeared to epitomize it (Knight 2013). In understanding the development of such innovations, one major starting point has been the economist Joseph Schumpeter's formulation of 'creative destruction', in which a group of people or a person develops an idea or invention into a new product, process or market, thereby replacing prior innovations (Schumpeter 1942). Breaking from static economic frameworks from his time, Schumpeter saw these waves of innovation in processual terms as explaining the dynamic change witnessed in capitalism (Ingham 2003).

As has been argued by innovation scholars, this change does not occur via only playing the lottery, where the probabilities of a bet are known ex-ante (Lazonick and Mazzucato 2013; Mazzucato 2013a). Rather, innovation embodies what scholars have called 'Knightean uncertainty': the odds of generating rewards from investment in innovation are unknowable

beforehand (Knight 1921; Lazonick and Mazzucato 2013; Mazzucato 2013b).¹⁸ In this view, playing probabilities will simply not do. Innovation processes instead necessitate direct confrontation with an ‘immeasurable risk’, which in turn requires long-term strategic commitments. This confrontation happens from the earliest stages of a process, often a long time away from the launch of a product or creation of a new market. The first steps in generating a new compound, for example, have been called by Gambardella (1995) the ‘most creative steps’ in drug development and contains a high level of technical uncertainty. As a process moves along, scientists and drug developers attempt to answer questions relating to a product’s different technical risks through further clinical testing and human clinical trials. By the final stages, such as in Phase III clinical trials, this prior testing can make it possible to place a probability of success for a given compound (Bleicher et al. 2003; Pisano 1997; Robbins-Roth 2001). We can thus think of uncertainty and risk existing along a continuum across an innovation process.

Taking on this uncertainty and risk is not a lone enterprise. Rather, as the ‘systems of innovation’ school of thinking has described, multiple organizational and economic actors across a society circulate and diffuse knowledge to generate innovation (Freeman 1995; Lundvall 1992). Among these actors is not just the private sector, which receives much of the attention (and to which we will return in due course), but the state, through a network of public sector organizations. Through its ability to mobilize funding from taxpayers, the state is viewed as taking on risks that private businesses otherwise would not (‘fixing market failures’, by conventional economic parlance). In the arena of drug development, for example, the state has been described as taking on the upstream science required to produce new compounds and therapies.¹⁹ Others argue, instead, that the role of the state in innovation goes beyond investments in basic science and research and ‘fixing market failures’. Rather, as Mazzucato has described, an *entrepreneurial state* is a potential lynchpin in driving innovation across sectors and national economies (Mazzucato 2013b). Mazzucato has identified several key features that constitute an entrepreneurial state, differentiating it from a state that only provides public goods such as basic science.

¹⁸ Refers to Frank Knight, an economist in the early 20th century. He elaborated the concept of uncertainty in his 1921 book *Risk, Uncertainty, and Profit*.

¹⁹ Multiple studies have identified the origins of particular compounds or broader therapeutic advances to the US state via their National Institutes of Health (Angell 2004; Sampat and Lichtenberg 2011). As I alluded to earlier, however, such a view of the state’s role in the innovation process for new medicines may be too narrow.

First, the state provides patient investment *across the upstream-downstream stages* of the innovation process. Through a network of decentralized public organizations, investment goes towards not only to basic science, but also to companies and projects with commercial potential (Mazzucato 2013b). In Mazzucato's view, this latter investment does not 'crowd out' private sector actors; rather, the state provides substantial resources to technology development in ways that 'risk-averse' companies do not. In the US state, for example, we find that the Small Business Innovation Research Program is a pivotal source of support for early-stage businesses in uncertain technological spaces (Keller and Block 2013; Mazzucato 2013b).

Second, the state uses this investment to take on 'technological frontiers', where overcoming radical uncertainty and technical hurdles can translate to entirely new business opportunities that were previously unforeseen (Mazzucato 2013b). For example, this risk-taking capital has produced new general purpose technologies on which entire new sectors of the economy, such as biotechnology, have been borne. Third, Mazzucato describes a state which sets the 'direction' for innovation, through a mission-orientation that far from 'market-fixing' actually *creates and shapes* markets to produce value and overcome challenges with broad social implications (Mazzucato 2013b; 2016). Public investment in green technologies illustrates the potential market and direction shaping powers of an entrepreneurial state (Mazzucato 2015).

Finally, an entrepreneurial state also governs the 'rules of the game' that mediate the relationship between public and private actors, and in turn can determine the extent to which an innovation 'ecosystem' is mutualistic (win-win) or parasitic (in which few actors extract more value than they put in to the process) (Mazzucato 2013b; 2016). The U.S. Bayh-Dole Act, which stipulates the rules by which publicly funded science can be patented, for example, is one such rule that I return to in chapter 3.

The frame of an *entrepreneurial state* encourages research that peels back the layers behind an innovation process and identify the extent to which public investment and risk-taking may have played a critical factor. In the domain of drug development, this concept has largely been applied at the level of the pharmaceutical industry (i.e. the emergence of biotechnology or the overall role of the NIH) rather than traced in the context of specific therapeutic areas. Few case studies of drug development have attempted to go beyond early-stage science to systematically explore the contributions of an *entrepreneurial state* as described by Mazzucato across the innovation process. Finding evidence of the state's contribution to hepatitis C drug

development and *sofosbuvir* specifically would shape our understanding of the division of innovative labor undertaken in the process.

Beyond public sector organizations, however, multiple types of private companies are also typically part of innovation processes. In the development of *sofosbuvir*, this includes biotechnology companies and incumbent pharmaceutical firms. Unlike the taxpayer-funded state, companies must direct retained capital from within their firm or attract capital from external sources in order to finance projects aimed at innovation. These requirements are subject to a vexing set of dynamics to which we turn our attention next.

1.3.2 Finance and financialization

Schumpeter's insight into the critical role of innovation in the economy, as I described earlier, was paired by his interrogation of the central function of credit money in the economy. He recognized that new products, processes or markets would not materialize on their own, but rather require the kind of credit investment that enables the experimentation, failure, and long-term learning characteristic of innovation (Ingham 2003). For Schumpeter, writing in the first half of the 20th century, banks – which he held to be the 'headquarters of capitalism' – would be the source of this credit money (Ingham 2003; Mazzucato 2013a).

Fast forward over the 20th and into the 21st century, and Schumpeter could not have foreseen the heterogeneous array of financial actors (venture capital, institutional investors, the stock market, public sector organizations) that now populate the landscape. This heterogeneity in financing is mirrored by firms at different stages of the product and business cycle, from early-stage start-ups without any sales, to businesses about to launch a product, to established incumbents with existing flows of profitability (Gompers et al. 2005; O'Sullivan 2006). Just as these businesses have diverse financing needs depending on their position in the life cycle, the expectations of different financial actors in turn pattern the strategies of businesses and the larger industrial structure. For example, Gary Pisano (2006) in his book *Science Business* has described the emergence of biotechnology companies from the late 1970s onwards, and the parallel growth of different forms of financing as these early stage companies pursued therapeutic development. Pisano dissects the inadequate nature of much of this finance: neither venture capital nor stock markets, in his view, provide the kind of long-term investment model needed to translate a complex scientific base to overcome the risk-laden hurdles of therapeutic development. His mapping of the biotechnology sector offers a view into how 'financial actors' can influence 'non-financial' actors involved in productive processes of drug development. Though he never

explicitly unpacks the underlying logics and institutions behind this impatient financial capital, Pisano tacitly points to a trend that has been described extensively elsewhere: *financialization*.

Drawing on multiple reviews of the concept, I take *financialization* to describe both a shifting ‘pattern of accumulation’ as well as a set of political-economic mechanisms to which this shifting pattern can be traced (Davis 2009; Krippner 2011; van der Zwan 2014). Scholars of financialization have documented the two distinct but related dimensions to this pattern of accumulation: one is the expanding role and profits of financial sector actors and short-term oriented trading markets, and another is the rising influence of shareholder control (and ‘maximizing shareholder value’) on corporate governance and strategy (Mazzucato 2013; van der Zwan 2014). Together, the existence of financial markets as vehicles for short-term betting and the influence of shareholders as the primary recipients of capital within corporations has privileged, as Krippner (2011) puts it, “a pattern of accumulation in which profits accrue primarily through financial channels rather than through trade and commodity production”. To understand the emergence and reproduction of this pattern, three central mechanisms have been highlighted – in addition to the (1) speculative dimension of financial markets and (2) the dominance of shareholders, scholars have linked (3) state actions to financialization. I describe these three mechanisms briefly here (see Table 1.2 for a summary). I also highlight the nascent but growing literature connecting financialization to the pharmaceutical sector, which has largely focused on the second (i.e. shareholder dominance) of these mechanisms.

Table 1.2 Potential mechanisms for financialization

	Description	Potential gaps in explanation
Speculation	Capitalists pursue capital accumulation through speculation in financial markets, based on betting on the future valuations of assets, creating vulnerability to disruptive events and cycles of bubbles and bursts.	Does not explain the institutional mechanisms by which speculation operates, such as the construction of assets that are the object of speculation and financial markets.
Shareholder control	Shareholders have displaced managers as the key agents of control over the capital allocation decisions of businesses since the 1970s, with a focus on share price in equity markets and distributions of capital ('maximizing shareholder value') in the form of buybacks and dividends over long-term internal investments; explains shifting corporate strategies oriented around financial markets.	Does not focus on implications for product-level trajectories and prices; instead, focuses largely on macro-industry or firm-level capital allocation strategies, and implies higher prices are due to maximizing shareholder value ideology but does not specifically map out how products are valued and priced
State governance	Policymakers beginning in 1970s responded to a constellation of fiscal and social crises by depoliticizing economic management through a series of governance decisions over interest rates, inflation, and regulation that led to the rise of finance (Krippner's thesis). One example: high interest rates in 1980s meant that companies could make more money in credit instruments than productive investments.	Explains the larger political-economy shifts towards the accumulation of capital by the financial sector, but does not relate this specifically with pharmaceutical sector or biomedical innovation; for example, the emergence of new kinds of financing (such as venture capital).

Speculation: One mechanism by which this shifting pattern of accumulation is argued to occur is the emergence and growth of speculative financial markets. By this view, investors aim to use the financial market to make short-term bets for near-term gains based on the selling of assets or trading of shares in a given company. This future-orientation creates susceptibility to 'external events', such as the introduction of a new technology or policy change whereby prices can swing based on the psychosocial dynamics ('herd effects') of traders (Kindleberger 1978, Minsky 2015, Shiller 2003;2014). When such manias occur, prices are severed from purported 'intrinsic values' (Shiller 2003; 2014). This literature offers two key insights: the future oriented nature of valuation strategies undertaken by financial actors and their consequent susceptibility to bubble and burst cycles. Others argue, however, that an understanding of financial accumulation requires a further analysis of the institutional dimensions underlying speculation (Krippner 2011; Leyshon and Thrift 2007). Leyshon and Thrift (2007:98) observe, for example, that the "bedrock of financial capitalism is *not* the spectacular system of speculation but some thing more mundane; that is, financial capitalism is dependent on the constant searching out, or the construction of, new asset

streams, usually through a process of aggregation, which then – and only then – allows speculation to occur”. This critique points to the need to analyze assets that underlie speculation, particularly knowledge assets in the realm of biomedical innovation, and the institutional dimensions of the construction and trajectory of such assets through financial markets.²⁰

Shareholder control: The second mechanism explored in explanations of financialization is the ascendancy of shareholders in governing corporate strategy, contrasting to an earlier period in which business managers more closely controlled capital allocation decisions. Scholars analyzing this mechanism argue that this shift has increased the orientation of non-financial firms to financial markets and thereby shaped business strategies (Davis 2009; Lazonick 2015). This shift is traced, in turn, to several factors (see Table 1.3 for a summary). One has been the growing scholastic view in the 1970s that shareholders, not corporate managers, could most efficiently allocate capital across the economy using share price as a core metric (Fama and Jensen 1983). This vantage was linked to the ‘principal-agency’ theory in law and finance, which posited that the ‘residual’ earnings of a corporation belong to the shareholder, because they have no market-determined or contractual guarantee of a reward (unlike workers with salaries, for example) (Fama and Jensen 1983; Jensen and Meckling 1976). Without uniting ownership with control over management, agency theorists have argued, managers have no incentive to return value to shareholders and could instead pursue inefficient or management-enriching strategies at the expense of the economic efficiency that ‘maximizing shareholder value’ could instead bring. This scholastic view linked with political-economic shifts, with institutional shareholders gaining greater power onwards along with the emergence of an active market for hostile takeovers in the 1980s enabling owners to place increasing pressure on managers to take measures to boost share price.

While these arguments from law and finance and political-economic shifts in the 1980s provide important context, I draw primarily from the literatures on changes in corporate governance and strategy that reinforced this shift towards shareholder control (Davis 2009; Lazonick 2010; 2015; Mazzucato 2013a). This literature has focused on the ways in which corporate governance and strategy has shifted to ‘maximize shareholder value’, with two dimensions central to the analysis. One has been the increasing move towards repurchasing a company’s own shares (‘share buybacks’) as a vehicle to distribute earnings to shareholders, while the other has been the

²⁰ I return to this analysis by focusing on Veblen’s conception of capital and assets in the next section (1.3.3).

increasing use of stock options and awards for executive compensation, thereby linking the interests of executives to shareholders using share price as a core measure of performance (Davis 2009; Lazonick 2014; Lazonick et al. 2016). I investigated and elaborated on the extent to which these strategies of capital allocation and compensation may have shaped the innovation process behind *sofosbuvir*.

Table 1.3 The shift towards shareholder control

Key factor	Description and time period
Scholastic arguments from law and finance	<ul style="list-style-type: none"> - ‘Maximizing shareholder value’ argued by law and finance scholars in the 1970s and 1980s as a way to create efficient capital allocation across the economy, with shareholders using share price in financial markets to evaluate the potential for sectors and firms (‘efficient market hypothesis’) to deliver growth. - Business managers expected to direct/disgorge ‘free cash flow’ from earnings (or ‘residual earnings’) to shareholders, with shareholders argued to be the only ‘residual claimants’ on a corporation’s earnings. - Aimed at resolving the ‘principal-agent’ problem, with business managers (agents) otherwise believed to use capital for ‘inefficient’ purposes.
Political-economic shifts	<ul style="list-style-type: none"> - Increasing influence granted to institutional shareholders through political-legal arrangements that concentrated shareholder ownership in pension and hedge funds - Active takeover market in the 1980s used as a vehicle for shareholder pressure, with companies with low share prices seen as vulnerable targets
Changes in corporate governance and strategy	<ul style="list-style-type: none"> - Increasing distribution of ‘residual’ earnings to shareholders, with SEC Rule 10-b-18 promulgated in 1982 permitting companies to distribute earnings to shareholders through buying back a company’s own shares (‘share buybacks’). - From 1980s onwards, executive compensation increasingly tied to stock-based pay, such as stock options and awards; executives, as major shareholders themselves, driven to ‘maximize shareholder value’

Note: I focused on the third set of factors (highlighted) in the course of my investigation.

A series of analyzes have examined the influence of this escalating shareholder orientation within the pharmaceutical sector (Andersson et al. 2010; Gleadle et al. 2014; Lazonick et al. 2016; Montalban and Sakinc 2013). These studies have centered largely on chronicling how large established companies are increasingly down-sizing their early-stage efforts (to mitigate the technical risks of drug development) and distributing their accumulated capital to shareholders, relying instead on small biotechnology companies to supply them with new potential products that can generate growth (Andersson et al. 2010; Gleadle et al. 2014; Montalban and Sakinc 2013). Lazonick (2015) has called this approach by large firms more broadly to be the ‘downsize and distribute’ model of corporate strategy in the name of ‘maximizing shareholder value’. These literatures thus also illustrate shareholder value to be a *distributive* project (Davis 2009; van der Zwan 2014): by directing the rewards of a collective process of production and innovation to a single class of actors – shareholders – other actors, such as workers and taxpayers, are seen to be

marginalized (Lazonick and Mazzucato 2013). In this view, a small group of financial actors engage in *value extraction*, by which shareholders accrue rewards disproportionate to the capital they risked into productive processes (Lazonick 2015).²¹ Like the literature on the entrepreneurial state in the setting of biomedical innovation, however, much of the analysis of financialization has focused at a macro-economy or sectoral level, with few cases of a product or firm-level view. This gap limits our understanding of the meso-level mechanisms and precise impacts of shareholder control on crucial goods, such as the pricing of medicines.

State action: A third mechanism described to underpin financialization is the role of the state, of which the most prominent work has been done by the economic sociologist Gretta Krippner (Krippner 2005; 2011). In her book *Capitalizing on Crisis: The Political Origins of the Rise of Finance*, she recounts financialization as less a deliberate outcome sought by US policy-makers, but an unplanned result of their attempt to respond to a unique constellation of crises that confronted the state beginning in the late 1960s and 1970s (Krippner 2011).²² In their response to crises such as inflation and slowed growth, policymakers turned over decisions to a state-constructed ‘de-politicized market’ through an array of governance choices related to monetary and banking policy. These decisions together produced the rise of finance. The maintenance of high interest rates by Federal Reserve chairman Volcker, for example, lured companies to direct more of their capital to financial instruments rather than invest in their businesses, one of the mechanisms by which non-financial firms became financialized (Krippner 2011). Taking a cue from her interrogation of the broader relationship between the state and financialization, I aimed to look at this relationship in a more narrowly confined matter, as it relates to biomedical innovation in the case of *sofosbuvir*. This meant observing the circulation and accumulation of capital across the *sofosbuvir* innovation process and following any potential connections between different state actors and the rules governing this flow of capital.²³

²¹ Lazonick (2015) has argued that ‘maximizing shareholder value’ is “a theory of value extraction that lacks a theory of value creation,” as the central focus is on the distribution of capital to shareholders through financial markets rather than on investments in organizations that can generate value.

²² Though I do not chronicle her full analysis here for the purposes of brevity, Krippner’s work to ‘bring the state back in’ to analyses of financialization is a pressing and important task in the realm of biomedical innovation, which I highlight in chapter six.

²³ As I describe in my methodology as well as in my discussion chapter (chapter six), I did not perform an exhaustive analysis of the regulatory apparatuses of the state as it relates to the financing of biomedical innovation – instead, I investigated the kinds of financing and capital allocation decisions that shaped my specific case, the innovation process behind *sofosbuvir*. I then noted what, if any, state policies and rule-changes may have in turn influenced those financing and capital allocation decisions. This ultimately presented a limited view of the state in relation to financialization, as I did not do in-depth research into

1.3.3 Capital and capitalization as power

Thus far, we have discussed the innovation process largely in terms of the state as well as financial actors, while only indirectly touching on the biotechnology and pharmaceutical businesses that are also part of the terrain. In this section, I draw on the economist Thorstein Veblen's analysis of business to address gaps in current conceptualizations of pharmaceutical companies in the innovation process (Veblen 1908a; 1908b). As I described earlier in section 1.1.3, the focus in drug pricing debates has largely been on the monopoly power of larger, established pharmaceutical companies. In this view, large companies pursue pricing strategies designed to maximize profits, and use their lobbying power over the state to maintain favorable intellectual property and pricing related rules. While the attention to the influence of pharmaceutical industry has produced important insights in the analysis of regulatory science and drug approval²⁴, similar work in the arena of drug pricing must extend our understanding of the position and interests of different business actors in the innovation process. An investigation of drug pricing requires analytical tools for questions that often go unanswered.

For example: (1) How does the control over knowledge – secured through patents (state granted 'monopolies') – function in business strategies at different stages of a product development cycle? For example, as multiple analysts have described, small biotechnology companies rarely produce profits from the sales of products, and yet can generate significant returns for their venture capitalist backers – indicating that the function of patents varies depending on the stage of the product development cycle (Birch 2016; Lazonick and Tulum 2011). (2) What are the pricing and valuation approaches that business actors use, and what does this tell us about the relationship between businesses and other actors in the innovation process? Business organizations pursue their pricing strategies within complex political-economic contexts that include competing businesses, the financial sector and shareholders, as well as potential buyers (i.e. government health systems (Gregson et al. 2005; Maldonado Castañeda 2016; Scherer 2004). (3) Finally, what are the specific logics of profitability and growth that structure the

the strategic interests and historical processes at stake in each domain of state policy and regulation. Further research focusing on the role of the state and the financialization of biomedical innovation at the level of the state and multiple firms and the broader sector – beyond a single therapeutic case – can redress this limitation.

²⁴ For example, Abraham and Davis have provided important historical and sociological insights into the ways that companies use their power to appropriate public agencies and bias the 'rules of the game' by which new medicines are approved (Abraham 2002; 2008; C. Davis and Abraham 2013).

strategies of business, beyond ‘maximizing profits’ – and how are these strategies shaped by potential competition and financial markets? As I indicated with the literature on financialization, business organizations operate in financial environments in which time-bound expectations shape their strategies (Lazonick et al. 2016; Rajan 2012). ‘Maximizing profits’ may be one part of the equation, but may not fully capture the calculations that guide companies to pursue certain business strategies.

To develop analytical tools capable of interrogating business organizations in the innovation process behind *sofosbuvir*, I turn to Veblen-inspired works which examine the ways that businesses accumulate capital and generate specific power relations in the economy.²⁵ In a period of rapid industrial change and concentration of wealth at the turn of the prior century, the economist Thorstein Veblen outlined a prescient dissection of capital and power in two articles in *The Quarterly Journal of Economics* in August and November of 1908 (Veblen 1908a; 1908b). Veblen viewed the power of the new businesses he was witnessing as resting not in new forms of productivity, as often assumed in the neoclassical economic theories of his colleagues, but more so in the means by which business interests deployed and extended their control over industrial knowledge to accumulate capital.

In pursuing what scholars have termed a ‘realist’ analysis of capital, Veblen (1908) had three key insights that, taken together, can provide a robust toolkit to dissect the innovation process and the pricing strategies that are entangled with it. I elaborate these three insights by drawing on Veblen’s original scholarship as well as a small group of political economists and science and technology studies (STS) scholars that have translated Veblen to biotechnology and pharmaceutical development (Birch 2016; Cochrane 2011; Nitzan and Bichler 2009; Veblen 1908b).

First, Veblen saw production to be a social process using and generating an array of what he called ‘assets’ in a ‘community’. These assets, could be tangible, such as material technologies,

²⁵ One growing area of contribution from anthropologists and sociologists of science and technology studies are the links between shifts in biomedicine towards a more molecular and genomic base to shifts in capitalism towards a more financialized mode of accumulation. This literature has centered on discussions related to ‘biocapital’, and other ‘bio-hyphenated’ concepts. Popularized in part by Sunder-Rajan’s book *Biocapital* as well as lively commentary by colleagues such as Joseph Dumit with his notion of *surplus health*, they have traced how the turn to the molecular (i.e. biomarkers, genomics, surrogate endpoints) is entangled with discourses of capitalism that abstract biomedicine away from the embodied health experiences of patients and towards the future-oriented, promissory force of financial value (Dumit 2012b; Helmreich 2008; Rajan 2006; 2012; Rose 2007). While I draw on their insights in the rhetorics of this dynamic, my interest in *sofosbuvir* is more oriented around the political-economic mechanisms along which capital and knowledge flows.

or intangible, such as knowledge (patents, for example).²⁶ Capital, in this view, materialized with the *ownership and control* over groupings of tangible and intangible assets by more powerful economic actors within the community (Cochrane 2011; Veblen 1908a).²⁷

Second, Veblen defined capital as a *quantified* form of control with a future orientation, because owners value their assets based on the *expected future stream of earnings* that can be derived from their ownership (Birch 2016; Muniesa 2011; Nitzan and Bichler 2009; Veblen 1908a). Business organizations and financial actors use *capitalization* exercises to value these streams of earnings, in which future earnings are translated into a present value to guide decisions over capital allocation (Muniesa 2011; Nitzan and Bichler 2009). Birch (2016) has linked the paradox of the biotechnology sector – most companies produce no products or sales but attract large flows of capital – to the ‘assetization’ of drug development, in which anticipated downstream prices and market valuations, not profitability, are the basis for investment (Birch 2016; Birch and Tyfield 2013). He illuminates the logics of assets by contrasting them with commodities – a comparison I highlight in Table 2.1 below.²⁸ Furthermore, capitalists not only anticipate capital in terms of future streams of earnings, but based on whether assets will generate a *differential* advantage against other capitalists (Cochrane 2011; Nitzan and Bichler 2009). In other words, capitalists pursue accumulation not by some absolute register, but by comparison against other opportunities (cost of capital, competing businesses, competing sectors). This conceptualization of assets informs my investigation into the ways pharmaceutical businesses manage, value, and struggle over assets in the innovation process.

²⁶ Assets are defined by the International Accounting Standards (IAS) as: “a resource that is *controlled* by the entity as a result of past events (for example, purchase or self creation) and from which future economic benefits (inflows of cash or other assets) are expected (International Accounting Standards 2016).

²⁷ Veblen (Veblen 1908b:525) described the process of increasing ownership and control in historical terms: “As the technological development falls into shape as to require a relatively large unit of material equipment for the effective pursuit of industry, or such as otherwise to make the possession of the requisite material equipment a matter of consequence, so as seriously to handicap the individuals who are not without these material means, and to place the current possessors of such equipment at a marked advantage, *then the strong arm intervenes, property rights apparently begin to fall into definite shape, the principles of ownership gather force and consistency, and men begin to accumulate capital goods and take measures to make them secure*”.

²⁸ Birch’s adaptation of Veblen’s work on assets highlights 1) the future orientation in the valuation of assets as well as the 2) distinct demand logics of assets, particularly in financial markets. This conceptualization enables an analysis of the ways in which financial actors value compounds along the innovation process, and explains the speculative bubbles and rushes that occur in drug development. For example, why did Gilead Sciences buy Pharmasset for \$11 billion in 2011? This vantage provides a way to answer this question.

These two points – capital as the ownership and control over assets as well as a quantified form of control – converge on a third: capitalization represents a relational form of social power. The capitalization exercises required to calculate future streams of earnings from owning intangible and tangible assets are far from simple pricing operations in a ‘natural’ market. Rather, as Nitzan and Bischler (2009) have elaborated in their ‘capital as power’ scholarship, methods of capitalization *translate a complex magma of social interactions* between capitalists and other social actors. For example, when a large incumbent pharmaceutical company is pursuing an acquisition of a smaller company, their analysis of the value of the smaller company’s assets is based in large part on their perception and anticipation that future buyers may be willing to pay for this asset. This assumes the rules and relations of power governing the exchange between the company and the buyer (often government health systems). In linking Veblen to the pharmaceutical industry, Gagnon (2016:596) interprets the implications of such an analysis, worth quoting at length here:

“Not only are productive assets capitalized in the process, but also any institutional reality is capitalized as well, be it social, legal, political, culture, psychological, or any thing else that can grant an earning capacity. Capitalization is therefore based not only on productivity but any institutional and structural power that confers control over the community to increase differential gains in the sphere of distribution (or in the words of Veblen, any capacity for vested interests to gain some thing for nothing)”

This conceptualization of capital and capitalization as translations of multiple forms of power that pattern the accumulation strategies of capitalists can be applied to biomedical innovation (Cochrane 2011; Gagnon 2016). The process of capitalizing assets is an almost continuous process in contemporary drug development: for example, intangible pharmaceutical assets far from approval are evaluated for their value through a web of financial markets and business organizations on a daily basis (any cursory look at the business section of the newspaper or the NASDAQ index illustrates this). The pricing of pharmaceutical assets, in this context, can be studied through unpacking the future-oriented ‘valuation strategies’ employed by these economic actors (Beckert 2011; 2014; Maldonado Castañeda 2016).

While this scholarship provides helpful tools with which to analyze pharmaceutical businesses, they have not been applied to specific empirical cases of drug development and pricing. The case of *sofosbuvir* offers an opportunity to test the utility of these concepts in an empirical crucible. Nor has Veblen’s original conceptions of assets, capital, and capitalization

been linked, in the context of biomedical innovation, to late-20th century shifts towards financialization that I reviewed in the previous section. Joining up Veblen with an analysis of financialization may provide the tools with which to fully understand the prices of *sofosbuvir* and the innovation process that produced them.

Table 1.4 Comparing Assets vs. Commodities

Assets		Commodities
Ownership relationship (over <i>future</i> stream of earnings, secured via political-legal contract)	Source of value	Exchange relationship
Can be intangible (knowledge, IP) or tangible (inventory, equipment)	Types	Typically refers to a tangible good or service
Prices goes up with higher demand (i.e. asset bubble in speculative rushes)	Demand logics in markets	Prices fall with increase in demand (depends on the type of ‘market’ – such as generic vs. patent/branded market in pharmaceuticals)
- Copyright over album - Intellectual property over compound structure	Examples	- iTunes version of the album on sale for \$17.99 - Generic pharmaceuticals

Source: Birch (2016)

1.3.4 The possibilities from synthesis: actors, mechanisms, and evaluation of outcomes

Each of the three threads – innovation and an entrepreneurial state, finance and financialization, and capital and capitalization as power – provided conceptual tools with which I investigated the innovation process and pricing behind *sofosbuvir*-based medicines. I returned to them iteratively throughout my research in the pursuit of building a synthetic representation of the innovation process. This analytical orientation towards my investigation offered three possibilities: (1) exploring the relationships between a triad of key actors rather than a single actor or state-business dyad, (2) a consideration of multiple political-economic mechanisms, and (3) a framework with which to not only describe the process but also evaluate its outcomes.

First, the literatures together gave me the tools with which to explore the potential roles of three key sets of multivalent actors in the innovation process – the state, finance, and business – as well as the relationships between them. Rather than locate pricing as a hermetically sealed matter for a single actor to determine or an outcome of a single relationship (state-business, for example), this triad motivated a search for the relations of power at play. By ‘multi-valent’ actors, I mean that multiple organizational types with different strategic interests and positions in the innovation process comprised each ‘set’ of state-business-financial actors contained. For example, I did not take the ‘state’ to be singular: though an entrepreneurial state is the explicit focus in the first thread, state actors appear in different forms vis a vis financialization as well as with

businesses – such as in governing financial actors (the SEC) and regulating pricing possibilities (health delivery systems).²⁹ I thus attempt to account for this heterogeneity across the triad.

Second, with a single case as a ‘strategic site’ of inquiry, I could test the multiple mechanisms offered by the three threads in explaining the *sofosbuvir* case and bring together the comparative advantages of each. The financialization literature offers a macro-economic and firm-level view of regimes of accumulation, yet questions of how specific assets are valued and priced largely falls from view. The literature on capitalization provides a way of studying this quantification process (i.e. pricing) as a set of ‘valuation strategies’ that also tell us about the relations of power constituting such strategies. The literature on the capitalization of assets refers, via Veblen, to a ‘community of assets’, but does not explicitly trace the role of the state. The conception of an entrepreneurial state offers one way to give ‘the community’ a more specific form with which to investigate the genesis and evolution of assets. Finally, though the entrepreneurial state helps explain the confrontation with Knightian uncertainty and brings the state into the upstream-downstream process, this literature alone cannot explain the trajectory of the innovation process through financial markets or the pricing and valuation of medicines by businesses. The literature on financialization and capitalization provide insights into this trajectory.

A final opportunity of this synthesis is an interrogation of the distributive outcomes at stake in an innovation process. Viewing innovation as a cumulative and collective endeavor between these actors, we can take stock of the actors that took risks in the process (and what kind of risks), as well as the actors that accrued the rewards in the process. This push towards evaluating the outcomes of an innovation process is emphasized in Lazonick and Mazzucato’s (2013) framework of the ‘risk-reward nexus’, which I explore in the case of *sofosbuvir*. Lazonick and Mazzucato (2013:1094) argue that that though “one might expect that those economic actors who take the risks of investing in the innovation process would be ones to reap the rewards of when the innovation process succeeds and suffer the losses when it fails”, this link is in fact broken in contemporary capitalist economies in which a small number of financial actors are able to reap outsize rewards. The extent to which this framework holds true in this case is made

²⁹ Rather than assume and reify a unitary view of the state, I view the state *a la* Bourdieu: a set of public organizations engaged in institutional processes producing and struggling over scientific, technological, and economic capital while also deploying a type of “meta-capital” that set the rules of the game for social spaces, which can alter the distribution of capital between actors in those social spaces (Bourdieu, Wacquant, and Farage 1994).

possible by mapping out the distribution of risks and rewards across the innovation process behind *sofosbuvir*.

Understanding this distribution aims at *evaluating the innovation process*. As Lazonick and Mazzucato (2013:1096) suggest, we can then assess “whether it (the given ‘risk-reward nexus’) supports or undermines the innovation process.” I measure this in two ways in the case of *sofosbuvir*. First, I evaluate the *direction* and *sustainability* of the innovation process. I use Stirling (2009) and Mazzucato’s (2016) conception that innovation has a direction – a set of end-outcomes around which a process may be aimed – that can be empirically assessed (i.e. the extent to which a process yields clinically significant therapeutic advances or incremental and me-too medicines). By sustainability, I consider the extent to which the process supports further innovation (i.e. the reproduction of positive directional outcomes, such as breakthroughs in other areas of biomedical innovation). Second, because I hold the innovation process to also include the deployment phase of the technology (see Chapter 2, section 2.1 for my definition), I measure its patient and public health impact. Such an evaluation entails assessing the ways in which health systems adopted the medicines and, in the context of an infectious disease, were able to (or not able to) mount a public health response.

1.4 Revisiting the research questions

Having reviewed the literature, we can now revisit the research questions guiding the investigation. The analytical possibilities I chronicled above provided the conceptual tools with which to answer the first question I had identified in section 1.2:

1. *How do the organizational and political-economic dynamics in an unfolding innovation process explain the pricing of sofosbuvir-based medicines for hepatitis C?*

Based on my review of the literature as well as Lazonick and Mazzucato’s ‘risk-reward nexus’, I also asked a second question that accounted for the importance of evaluating the outcomes of the process:

2. *How were the risks and rewards of sofosbuvir’s development distributed across its innovation process, and what were the outcomes for the direction and sustainability of innovation as well as for patients and public health?*

I mapped the data used to answer the second question along the innovation process and returned to take stock of the outcomes in chapter 6. Before I describe the research design and methodology used to collect the data to answer these research questions, I first provide a brief primer into the target of *sofosbuvir*-based medicines: the hepatitis C virus. This primer will

provide helpful context within which other dynamics of the innovation process can be interpreted.

1.5 A shadow epidemic and the search for a cure: a primer

The human struggle against hepatitis C has endured for decades, with the virus assuming a secure – but not unassailable – position. Understanding this position from three angles – its silent and dangerous course in the body, its spread and transmission on a global scale particularly among vulnerable groups, and the molecular innovations and vulnerabilities that has shaped the search for therapies – provides important context for any sociological diagnosis of the *sofosbuvir* case. These three dimensions (see Table 1.3 for a summary) serve as a technical primer to support both the comprehension of the data and evidence and as an interpretation of the relative significance of core flanks of the argument.

Table 1.5 Key dimensions and features of hepatitis C

Key dimension of hepatitis C	Specific features
Chronic infectious course through the liver	<ul style="list-style-type: none"> - Virus is transmitted via the blood, primarily injecting drug use. - Scars liver tissue (fibrosis) over the long-term. - Can take 5-20 years for patient to reach end-stage liver disease, which is fatal.
Global epidemic of social disadvantage	<ul style="list-style-type: none"> - 150 to 170 million infected globally 350,000 die each year. - 3.5-4.7 million estimated to be infected in the US; 14 million in Europe. - Affecting patients in high and low income countries, disproportionately affecting vulnerable populations such as those incarcerated, people who inject drugs, and co-infected with HIV.
Therapeutic search	<ul style="list-style-type: none"> - Virus has several key proteins which, when targeted, eliminate the virus from the bloodstream by halting its replication. - Virus does not replicate outside the body, making drug testing and development initially very challenging. - Virus has a high error rate while replicating, leading to multiple subtypes (called genotypes), for which combination of compounds are often needed to treat the virus in order to target multiple proteins. - Therapies prior to <i>sofosbuvir</i> (interferon) had high levels of toxicity and low levels of cure, with patients only taking the treatment in the later stages.

1.5.1 A chronic infectious course through the liver

The first point of context: the hepatitis C virus is infectious, transmitted via the blood, but also *chronic*, in that the primary damage wrought by the pathogen is the scarring of the liver tissue over the course of many years (Afdhal 2004).³⁰ The transmission route for infection has typically followed two courses: (1) through blood transfusions before the early 1990s, when countries began instituting routine screening of blood banks for hepatitis C after the discovery of the virus in 1989, and (2) via injecting drug use with non-sterile syringes (Alter 2013; Chen and Morgan 2006; Rosen 2011b).³¹ In the early months after infection, patients do not experience any immediate symptoms and often are unaware of the pathogen. This asymptomatic course can go undiagnosed for years, unless patients are tested using basic antibody screening (Rosen 2011a).

The cause of this curious course of disease is due to the way the virus, while proliferating itself, instigates the body to attack its own liver. Rather than directly killing liver cells, the virus enters liver cells, replicates in large numbers, and spreads to neighboring liver cells (Rosen 2011a; Sulkowski and Thomas 2005). This invasion triggers an immune response of the body's own defenders, which attracts a variety of cells to the sites of injury. As the body attempts to heal these sites and contain the region of inflammation, liver tissue becomes riven with lesions and scars (Bedossa and Poynard 1996; Ge and Runyon 2016). This pathophysiological process of liver scarring is called *fibrosis*, which over time disfigures the orderly architecture of the liver into a state known as *cirrhosis* (See Figure 1.1). If a patient is diagnosed with the infection, a patient's liver is scanned in order to 'stage' the tissue on this continuum of fibrosis to cirrhosis to indicate the severity of disease progression. A *cirrhotic* liver – without its normal structure – cannot carry on with its crucial functions.

If we think of the liver as a giant processing plant at the center of a diverse economy of biochemistry – manufacturing proteins that clot our blood and maintain our blood pressure, storing and transforming energy sources, and protecting our blood stream from toxins– the devastating consequences of a cirrhotic liver come into full view (Chen and Morgan 2006; Rosen 2011a). As the disease progresses, a patient may experience intense fatigue, accumulation of fluid in the abdomen (called *ascites*), and a number of other physical signs and symptoms; without

³⁰ *Hepatitis* means literally 'inflammation of the liver'. Hepatitis C is related to hepatitis A, B, and E in that they are all viruses that affect the liver, but via different etiologies and pathophysiologic pathways which I do not detail here.

³¹ Sexual transmission has also been documented, but accounts for a small percentage of transmissions.

screening, patients may only be diagnosed at a more advanced stage when these physical changes have progressed (Rosen 2011a). Patients in the late stages of hepatitis C require hospitalization and liver transplants, may progress into liver cancer, and eventually die without treatment. But this process takes time and does not happen to everyone: anywhere from 5-20 years on average for patients, with estimates of 20% reaching the later cirrhotic stages (Rosen 2011a; Sulkowski and Thomas 2005). This duality of hepatitis C – with both potentially deadly consequences but also slow progression – means that the virus carries large scale patient and public health implications emulating an infectious epidemic (a transmissible pathogen, eventual mortality, stigmatization upon diagnosis of infection), but without the political emergency dynamic spurred by epidemics such as HIV/AIDS or Ebola (high velocity of mortality with widespread fear).

1.5.2 A global epidemic of social disadvantage

A second point of context relates to the populations affected the virus. The disease disproportionately affects populations down the gradient of poverty and relative political power. Particular patient populations - low-income patients, incarcerated peoples, people who inject drugs and those co-infected with HIV/AIDS – have higher infection rates than the general population (Beckman et al. 2016; Ward and Mermin 2015). This disproportionate risk travels globally, following the spread of the virus. The WHO estimates that 150-170 million are infected with the virus, with 350,000 dying each year (Hagan and Schinazi 2013). In Europe, 14 million are infected with the virus; in the UK itself, about 210,000 (Gornall et al. 2016; WHO 2015). The US has an estimated 3.5-4.7 million infected by the virus as of 2014, with the virus killing nearly 20,000 patients per year – more than all other infectious diseases combined, including HIV/AIDS (Edlin et al. 2015; 2016a).

Like HIV/AIDS but unlike diseases like tuberculosis, hepatitis C has affected populations in high, middle, *and* low-income countries (Hagan and Schinazi 2013; Momenghalibaf 2014; WHO 2015).³² The large numbers of infected persons, along with their disproportionate share in vulnerable populations, means that public health systems have been at the center of the response to the virus and the advent of new curative treatments (Chahal et al. 2016; Iyengar et al. 2016; Ward and Mermin 2015). In contrast to rare diseases affecting small numbers, or even diseases

³² The presence of populations in high-income countries meant that companies saw a market, unlike with diseases such as tuberculosis where infection is concentrated in low-income settings. I do not address the implications of hepatitis C pricing in low-income countries at great length, though I will refer to this briefly in chapter 6.

that in the US receive large coverage from private insurance (such as diabetes), hepatitis C – as an infectious killer that unevenly affects populations without private insurance – requires resources and commitment from the public sector.

1.5.3 Searching for therapies

Third and finally, the molecular biology of the virus – its structure and strategies for replication at its most basic level –has made it both a *stubborn* but also a *vulnerable target* for drug development. The hepatitis C virus is made of a single strand of genetic material; this genetic material replicates and translates into the ten proteins that compose the progeny of the virus (Scheel and Rice 2013). Of these ten proteins, three are used to make the structure of the progeny hepatitis C virus and are thus dubbed the “structural proteins”, whereas the other seven are used to make a copy of the genetic material for the next generation and are called the “non-structural proteins” (Lindenbach and Rice 2013). These non-structural (‘NS’) proteins, specifically NS3/4, as well as NS5b and NS5a, have been proven to be targets for drug compounds because of their ability to halt the replication process (Rice and Saeed 2014). *Sofosbuvir* targets the NS5b protein, which is considered to be the central protein in the viral replication cycle (Sofia et al. 2010).

Unlike the HIV virus, which integrates its genetic material *into* the host immune cells, the hepatitis C virus takes the new copy of genetic material and exits the liver cells, looking for new liver cells to fall prey (Lindenbach and Rice 2013). On the one hand, this replication approach has made the virus vulnerable to elimination, as targeting the viral proteins could remove the virus from the blood stream by halting its further replication. Patients could be cured of the virus, unlike with HIV, which remains in the bloodstream even with current treatments.

Yet on the other hand, the error-ridden nature of its replication has made hepatitis C stubborn to intervention. Notably, the virus replicates without a robust proofreading function, meaning the virus has generated a proliferating number of subtypes that are categorized into six known *genotypes* (Dorner et al. 2013; Scheel and Rice 2013). This means that drug compounds have to eliminate virus at a high level from the bloodstream in order to reduce the risk that surviving viral progeny can gain resistance against a given compound. For this reason, patients with different genotypes of hepatitis C have typically required different *combinations* of multiple treatments in order to attack the virus at several points (Rice and Saeed 2014). In addition to high rates of resistance, another blockade stood in the way of researchers: for unknown reasons, the

virus did not grow in cell cultures outside the human body, making it difficult to test potential compounds for their anti-viral effect in pre-clinical research (Bartenschlager et al. 2016).³³

This combination of high resistance and the difficulty of testing compounds meant that patients through the 1990s and 2000s were left with few options (Groopman 1998). Until *sofosbuvir*-based treatments, patients typically were prescribed *interferon*-based treatments (Heim 2013). Interferon is a protein that the body's cells release to 'interfere' with foreign invaders such as viruses, and increasing its potency aimed to eliminate the hepatitis C pathogen (Isaacs and Lindenmann 1957). However, much like chemotherapies for cancer, interferon is toxic for patients, with severe side effects (Heim 2013). Furthermore, patients had to bear weekly injections for 48 weeks (Heim 2013). The initial interferon-based therapies in the 1990s and 2000s reached a cure rate in only 20-50% patients, defined as the clinical endpoint of *sustained virologic response* (SVR) (Heim 2013).³⁴ Facing this long and difficult haul, many patients declined treatment until the late stages of disease (Groopman 1998).

The drug development opportunity was clear and urgent: directly attacking the virus, rather than using the indirect method of boosting interferon, could potentially lead to greater potency and lower side effects – and an eventual elimination of the virus (De Clercq 2005). Scientists followed the conventional research and drug development pathways (see Table 1.1) to test potential antidotes against hepatitis C, with pre-clinical research involved in identifying potential compounds that could target potential vulnerabilities in the virus and promising compounds moving into human clinical trials. The culmination of the multiple organizations and scientists navigating these challenges in pursuit of an antidote, however, were shaped by a series of political and economic dynamics. These dynamics foreground my research.

In summary, three crucial dynamics of the hepatitis C virus from its scientific and clinical dimensions are relevant to understanding the case. First, hepatitis C has a chronic-infectious course in scarring the liver that takes a long period of time and in a proportion of patients but has potentially deadly consequences. Second, the virus affects large numbers of people particularly among vulnerable populations, creating a matter for public health and public policy concern. Finally, the biological properties of the virus have made it stubborn to treat but also amenable to

³³ I document this technological challenge in chapter 4, and the role of a risk-taking state in overcoming the hurdle.

³⁴ SVR is defined as the failure to detect virus for 3 months after the completion of treatment and is equivalent to 'cure' – long-term studies have shown an exceedingly small percentage of patients (less than 1%) remitting after reaching SVR (Trepo 2013).

complete elimination. With this primer, we can now encounter the methodology used to engage with the research questions this dissertation poses.

Box 1.1. Clinical trial process in drug development

After pre-clinical research is completed, a compound may be deemed to be ready for clinical trials in humans. Before beginning clinical trials, companies usually file for patent approval³⁵ from the United States Patent and Trademarking Office, and their compounds are judged for being *useful, novel, and non-obvious*³⁶ (Angell 2004; Pisano 1997). To begin clinical trials, a pharmaceutical company files an investigational drug application (IDA) with the Food and Drug Administration. Trials proceed in three main phases before approval, with a fourth occurring afterwards:

- Phase I trials establish safe dosage and investigation of metabolism and side effects by testing in normal volunteers.
- Phase II trials investigate the drug in comparison to placebo, usually with a small number of patients with the relevant disease or condition. Drugs are given at various doses.
- Phase III evaluates the safety and *effectiveness* of the drug in much larger numbers of patients (hundreds to tens of thousands) by comparing it against the current standard of care. **FDA approval usually rests on these Phase III ‘registration’ trials.**
- Phase IV trials occur *after* FDA approval as post-marketing studies that survey for adverse reactions and further analysis of efficacy.

³⁵ Secrecy of the drug is not possible once clinical trials begin, so patents at this early stage ensure monopoly protection on their invention. However, the regulatory process also cuts into this monopoly period, incentivizing industry to push regulatory bodies to speed up their review process (Angell 2004).

³⁶ *Non-obvious* refers to the idea that the invention must go beyond what would have been the next logical step in the inventive process by some one trained ‘in the useful arts’.

Chapter 2. Research Design and Methods

A Case Study of Pricing through an Innovation Process

“There are an infinite number of facts about the motorcycle, and the right ones don’t just dance up and introduce themselves. The right facts, the ones we really need, are not only passive, they’re damned elusive, and we’re not going to just sit back and “observe” them. We’re going to have to be in there looking for them...The difference between a good mathematician and bad one, is precisely this ability to select the good facts from the bad ones on the basis of quality. He has to care!”

- Robert M. Pirsig (1991:279), *Zen and the Art of Motorcycle Maintenance*

In my second chapter, I describe the rationale and structure of the research design for answering the two questions that guided my investigation. I begin by chronicling a single case study-based research design and articulating the reasons for specifically selecting to focus on *sofosbuvir*’s innovation process (section 2.1). I then describe which data sources I used to construct the case study, the strategies I used to collect the data (section 2.2), and my approach to interpretation and analysis of the evidence I accumulated (section 2.3). Pirsig’s admonition shaped my iterative practice to data analysis, whereby I alternated between the evidence and data I collected and the analytic resources I chronicled in chapter 1 in order to progressively arrive at the answers contained in this dissertation. The chapter ends with an anticipation of limitations in my research design.

2.1 Case study design

In this section, I describe why I employ a single case study design as the vehicle through which to collect and interpret data to answer my research questions. Then I outline the parameters and key definitions that bound my object of analysis in the case study. I conclude by detailing the specific reasons for selecting the innovation process behind *sofosbuvir*-based medicines as the case for investigation.

2.1.1 Why a single case study

As I described at the end of chapter 2, two research questions animate my investigation. First, how did the organizational and financial dynamics of the innovation process for *sofosbuvir*-based hepatitis C medicines unfold to explain its pricing? Second, how were the risks and rewards distributed across this process and what were its attendant outcomes for innovation and public

health? A single case study is well-suited to answer such *how* questions, in which as Yin (1984:23) puts it, “the boundaries between the phenomenon and context are not clearly evident”. I aim to re-embed an analysis of the phenomenon of pharmaceutical pricing and innovation within the political-economic contexts in which it occurred. Though I appraised the literature to gain a sense for these contexts (such as financialization) prior to the research, their influences were not self-evident. I held them more as tentative frames open to elaboration and revision, with the answers emerging only by building the case study itself.

Furthermore, my research aim was not to control variables to validate hypotheses; rather, my questions targeted “a contemporary set of events, over which the investigator has little or no control” (Yin 2009). Rather than pursue a comparative method across several cases, or test a hypothesis among a large N set of cases, my goal was to apply sociological and political economy analysis to explain a set of outcomes (pharmaceutical pricing and the risks and rewards of the innovation process) and thereby make sense of a given case of interest. This focus in turn afforded me the opportunity to trace connections that could in turn be potentially used to interrogate other cases or used to generate theory in a larger N set of cases (Johansson 2003; Stake 1995).

2.1.2 A case study of what? Defining the object of study and its parameters

In a single case study design, the selection of the case is a crucial research choice that frames the opportunity for contribution. But before I articulate my reasons for selecting the particular case, however, I need to first answer another question: “a case of what?” Even though the boundaries within the case (such as between actors, or between phenomenon and context) are at stake as the research unfolds, I must aim my investigation at what Stake (2005:444) calls the “specific one” – a discrete object which marks the provisional bounds of the study. As Stake describes, “if we are moved to study it, the case is almost certainly going to be a functioning body” (Stake 2005:444). For example, a case study of pharmaceutical pricing and innovation could consist of, for example, a single drug company, a single drug, or a single relationship between a company and a government. Given my sociological orientation and the research questions derived for my study, I define the “specific one” under examination in this dissertation to be an *innovation process* behind the *sofosbuvir*-based medicines in which I trace the *relational* dynamics between multiple organizational actors that shape pricing. Each of the frames that shape my object of study –*processual* and *relational* - requires further resolution.

I draw on the literatures described in chapter 1 to articulate six parameters for analyzing an innovation process in pharmaceuticals. First, I first define innovation in pharmaceuticals as a process that generates improved clinical outcomes rather than a ‘me-too drug’ that received regulatory approval based on minimal therapeutic benefit from the existing standard of care (Avorn 2004; Gagne and Choudhry 2011).³⁷ This links to the notion that innovation has a *direction* in which new therapies can address health challenges facing patients and populations (Mazzucato 2016; Stirling 2009). As I have already indicated, *sofosbuvir* represents a major clinical advance by offering a cure in nearly all the patients that take the medicine. I aim to trace the key inputs that made this advance possible, as well as the extent to which directional outcomes – of improved patient as well as public health outcomes – were realized.

Second, I view this process as occurring across upstream-downstream stages, beginning with early science and onwards into *deployment* of a medicine (Freeman 1995; Lundvall 1992).³⁸ I intentionally include deployment, which breaks with conventional “R&D” accounts of pharmaceuticals, because this is the stage in which patients and public health systems stand to benefit from the higher quality medicines. Examining the extent to which potential patient and public health benefits are realized provides a crucial measure of the outcomes of the process.

Third, I study pricing and valuation along this process, specifically searching for ‘strategic sites’ at which prices are shaped in the upstream-downstream process. Though I take the launch prices in the US as a central query, I contextualize this launch price with the different valuations made by venture capitalists, potential acquirers, and the stock market earlier in the innovation process (Beckert 2011; Birch 2016; Maldonado Castañeda 2016; Veblen 1908b).

³⁷ Typically, the unit cost dimensions of an innovation outcome are also included within definitions of innovation itself. In this case of hepatitis C, however, I take economic efficiency gains (such as generation of better quality products at lower unit costs) as part of the contested terrain to be examined in this dissertation and thus do not include it directly in my definition. In other words, as I described in the ‘value’ argument in chapter 1, the very underpinnings of the economic valuation of pharmaceutical innovation are up for debate.

³⁸ I draw on two leading “systems of innovation” scholars, whose definitions of innovation include the diffusion phase as intrinsic to understanding the process. Freeman (1995) defined innovation as occurring within a “network of institutions in the public and private sectors whose activities and interactions initiate, import, modify and diffuse new technologies” and Lundvall (1992:2) expressed the process as “the elements and relationships which interact in the production, diffusion, and use of new and economically useful, knowledge”. I use the term “deployment” in this dissertation as a more intentional form of diffusion because *sofosbuvir*-based medicines, unlike an iPhone or other consumer technology, are a curative medicine for an infectious epidemic disease for which delivery systems are available and an explicitly defined market (infected patients) are waiting to use the medicine upon approval and manufacturing.

Fourth, I parallel Lazonick and Mazzucato (2013) in viewing innovation as a product of cumulative and collective efforts involving past and present knowledge contributed by multiple organizational actors. This means tracing past scientific and technical knowledge contributed to the innovation process as well as examining the roles of multiple public and private organizational actors involved in the innovation process.

Fifth, and finally, because I take innovation to be an uncertain process as defined in chapter 1, in which these multiple actors are taking risks for uncertain rewards, any analysis must account for these specific risks and rewards (Lazonick and Mazzucato 2013). I define risks to be the contribution of funding and capital (whether public or private) as well as innovative labor (taking on scientific and technical challenges of different qualities along a process), whereas I define rewards to be financial gains (revenues, taxes, capital gains) and health improvements (patient and public health outcomes and improvements). Understanding this risk-reward nexus can inform our assessment into the *sustainability* of the innovation process – the extent to the process generates further resources and capital for research and development into other areas of unmet medical need.

A sixth parameter is that innovation processes are mediated by the *geographic context* in which they unfold. This spatial awareness draws on science and technologies studies as well as the varieties of capitalism scholarship in political economy (Rajan 2006; Stuart and Sorenson 2003; Birch 2016; Hogarth 2017; Hall and Soskice 2001). Because the innovation process behind *sofosbuvir* almost all took place across U.S. public agencies and companies, my investigation is marked by several features of the U.S. ‘innovation system’ with regards to biomedical research. First, the U.S. government has invested significant sums in biomedical research, primarily through their National Institutes of Health, that has underpinned robust de-centralized networks of university laboratories as well as spurred scientific breakthroughs (Block and Keller 2009).³⁹ Second, over the past three decades, the U.S. has developed a sizeable venture capital sector (with hubs in Silicon Valley and Boston) that have backed nascent biotechnology enterprises at their early stages of development (Pisano 2006; Lee and Dibner 2006; Hogarth 2017). Third, scholars have noted the differences between national economies with regards to access to capital for corporations, whereby U.S. based companies (such as Gilead Sciences) are shaped by more short-term oriented capital within stock-markets as opposed to their German and Japanese

³⁹ Between its founding in 1938 to 2011, the NIH budget towards scientific and biomedical research has totaled \$804 billion in 2011 dollars (Lazonick and Mazzucato 2011).

counterparts, where a bank-dominant system allows for access to more patient forms of capital (Hall and Soskice 2001; van der Zwan 2014). Fourth, the regulatory apparatus within the Food and Drug Administration (FDA) and fragmented U.S. health system generally privileges the adoption of new technologies through accelerated approval pathways as well as limitations in drug pricing regulation in contrast with European countries, where national health systems tend to have greater bargaining power and regulatory authority (Kesselheim 2011; Kesselheim 2016; Davis and Abraham 2013).⁴⁰ As with any single case study based research, these geographically specific features will bound my investigation and the interpretation of findings, with the caveat that the innovation process may have unfolded differently if it had occurred in a different geographic context. Considering these hypotheticals is beyond the scope of the dissertation, but following the case through the U.S. context can provide a specific chronicling of how its specific features shaped the innovation process and drug prices.

Table 2.1 Parameters of the innovation process

Parameter	Implication for case study data collection
Generation of therapy representing significant clinical (and public health) advance	Identify the qualities of the product innovation and trace the actors and steps that made these qualities and directional outcome possible.
Upstream-downstream stages, including deployment	Trace early stages of hepatitis C research and drug development history and follow it to present-day period of treatment deployment.
Pricing and valuation	Follow mechanisms of pricing and valuation at locations along the upstream-downstream innovation process, with a focus on understanding the market launch price
Cumulative and collective effort with multiple organizational actors	Identify multiple public and private actors involved in the innovation process, as well as scientific and technical contributions that made discovery and development of <i>sofosbuvir</i> possible
Risks and reward nexus	Account for the financial and scientific/technical contributions across the process, as well as the financial and health rewards that were the outcomes of this innovation process
Geographic context	Follow the specific elements of how the geographic (regional or national) context shapes the innovation process (in this case of <i>sofosbuvir</i> , a U.S. based context).

⁴⁰ It is worth noting that the boundaries between the U.S. context and the rest of world with regards to regulation are often blurred by the influence that multinational pharmaceutical corporations can exercise. For example, the pharmaceutical industry has sought to increasingly 'harmonize' regulatory pathways by influencing both US and European regulatory authorities (Davis and Abraham 2013). Additionally, the launch prices set in the U.S. are typically discounted in Europe by 10-20%, meaning that the initial U.S. launch price becomes a reference point internationally (Kesselheim 2016).

Besides focusing on innovation as a *process* based on these six parameters, the other major consideration of my research design is to view this process in *relational* terms. By relational, I draw on Emirbayer's (1997) conception in which relations between actors or units are held to be the object of analysis, with these relations unfolding as processes rather than existing as static ties among inert substances (Abbott 1996). This emphasis aims to depart from the blind spots which have often confounded the debate over pharmaceutical development and pricing. These blind spots, which I identified in chapter 1, parallel critiques made of *substantialist* modes of research, in which 'substances' such as single, atomistic actors constitute the fundamental unit of inquiry rather than relations.⁴¹ In such modes of research, atomistic actors are deployed as pre-determined entities in research, thereby failing to capture the multiple dynamics of social life.⁴²

By contrast, a preferred relational approach within the case study allowed me to map sets of relationships over time. Rather than consider monolithic entities such as the 'state', 'business', and 'financial capital', I allowed my methods of data collection and analysis to reveal differentiated, multivalent actors along each axis of analysis as illustrated in Figure 2.1. For example, rather than focusing only on Gilead, I also related Gilead to small biotechnology companies such as Pharmasset. Additionally, I avoided an analysis of Gilead and its hepatitis C pricing in ahistorical terms, and instead traced the evolution of its business and mapped the sets of relationships (such as with the state and financial sector) which in turn shaped its hepatitis C strategy.

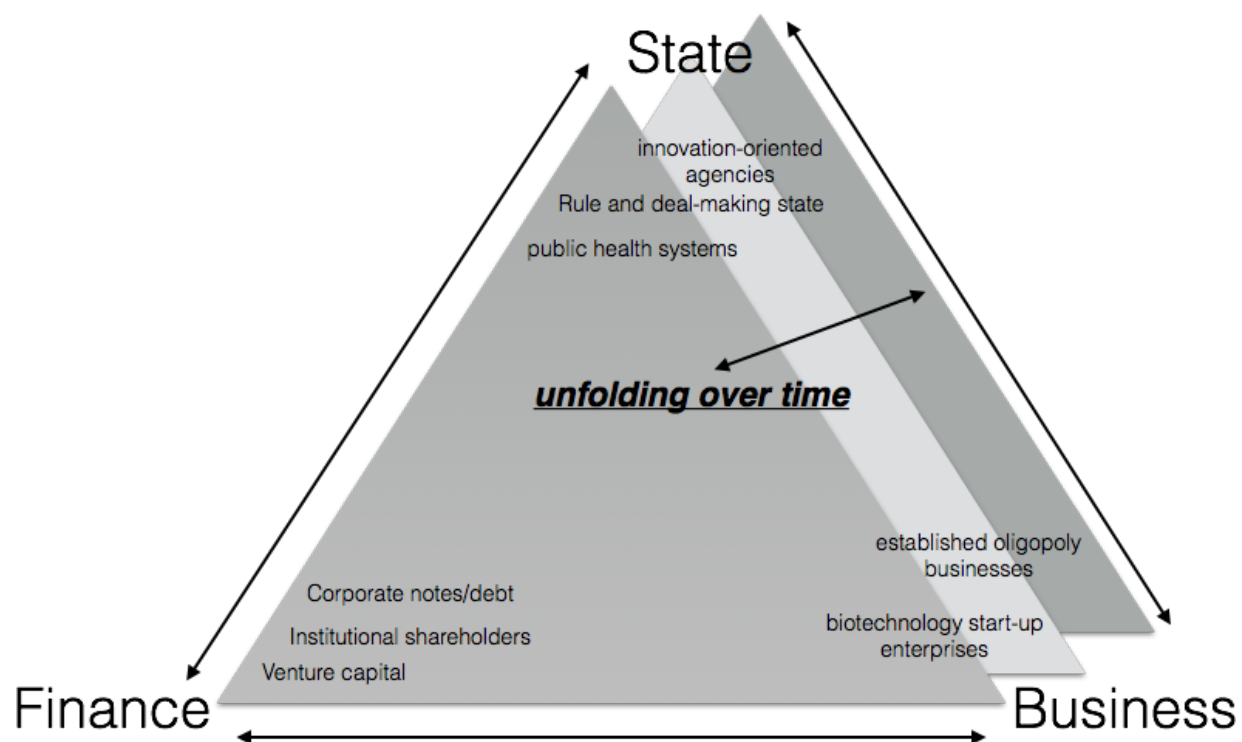
In keeping with this orientation towards analysis, I conceived of power not as atomized quanta attached to single actors to increase or decrease, but rather as a relational concept that emerges and evolves with the positions occupied by these social actors. Emirbayer (1997) explains such a treatment of power: "far from being an attribute or property of actors, then, power is unthinkable outside matrices of force *relations*; it emerges out of the very way in which figurations of relationships [...] are patterned and operate." Rather than assemble an elaborate

⁴¹ Emirbayer (1997) illustrates two pathways by which substantialist research typically proceeds, with each possessing critical limitations. One is a self-action pathway, in which actors are substances propelled by rational interests (as witnessed in rational actor theory), and an inter-action pathway in which actors or units are held as unchanging entities in which action takes place among these unchanging entities akin to Newtonian mechanisms (as in many variable-based quantitative studies).

⁴² Desmond (2014) highlights three critiques of substantialist modes of research: (1) imposing static and atomistic categories in place of intertwining connections; (2) dealing in 'groupism' rather than tracing the relations between groups, and (3) 'process-reduction' as opposed to unpacking the processual dynamics of social life.

taxonomy of power with multiple metrics or pursue a rank ordering of different kinds of power, my aim was to describe these ‘matrices of force relations’ and how they shape the innovation process. For example, the strategies of small biotechnology companies as well as established pharmaceutical companies can only be understood vis-à-vis their shifting positions over time with financial actors such as venture capitalists and shareholders. This view of power also emulates Veblen’s analysis of capital which I reviewed earlier, in which multiple relations of power get translated into the capitalization exercise used by economic actors.⁴³ Armed with this relational approach as central to my research design, I could trace the unfolding of an innovation process (defined by parameters set out earlier) to locate and follow the mechanisms and relations of power that produced *sofosbuvir*’s prices and a particular distribution of risks and rewards.

Figure 2.1 Mapping a triad of multivalent actors and relationship across time



2.1.3 Why the innovation process behind sofosbuvir-based treatments? Justifying the selection

Having justified an individual case study design focused on a unit of analysis that is process-based and relational in nature, we can now articulate the reasons for the selection of the

⁴³ See Chapter 1, section 1.3.3.

specific case. Stake (1998:236) points to this as the hallmark of any case study research design: “As a form of research, case study is defined by interest in individual cases, not by methods of inquiry used”. The interest in this individual case was based on three pieces of rationale, which I draw from different methodological and sociological scholars. First, the case fulfilled key operational criteria of the phenomenon in question (Yin 1994:91). Second, the case “looms large” over debates in pharmaceutical pricing and innovation (King and Sznajder 2006:767). Third, the case presented an “opportunity to learn” with uncommon access to data and social networks involved in the innovation process (Stake 2005:451). Taken together, these reasons align with my aim of explaining outcomes in a single case rather than testing theories in a set of ‘representative’ cases.

Sofosbuvir-based treatments posed two key operational criteria of the larger phenomenon under question: (1) *sofosbuvir* represented a true clinical breakthrough with public health implications and (2) their prices became the subject of intense social and political contestation. *Sofosbuvir*-based treatments created a drastic shift in treatment possibilities for hepatitis C patients: while prior regimens required six to twelve months of treatment and offered only 50% response rates with high rates of side effects and toxicities, *sofosbuvir*-based regimens have offered nearly 100% cure rates with few side effects after only three months of treatment (Hoofnagle and Sherker 2014; Ward and Mermin 2015). This clinical advance required scientific and technological advances over a significant period of time, meaning an innovation process existed which could be investigated. This trait is unlike many medicines that have prices deemed to be high but are the result of gaming the intellectual property system and not new scientific and technological labor, such as the prominent case of insulin in which prices continue to rise even though insulin’s discovery was decades ago (Greene and Riggs 2015).

The prices of *sofosbuvir*-based treatments also ignited a wide-ranging social struggle over treatment access and valuation. Unlike other prominent cases, Gilead’s pricing could not be explained away by maneuvers of a single business unit in acquiring previously approved or off-patented medicines (Armour and Rockoff 2016).⁴⁴ Nor could criminality be used as a central explanation. As a staff member of a US Senator shared with me, “you won’t find any thing orange jump-suit worthy here”, suspecting that I had been looking for incriminating evidence when

⁴⁴ Two cases of price gouging which drew public attention and indignation in 2015 and 2016, Turing Pharmaceuticals and Valeant Pharmaceuticals, have been subject to US Congressional scrutiny, with senior leadership in both companies coming under scrutiny. See “Valeant, Turing Boosted Drug Prices to Fuel Preset Profits” in Wall Street Journal on February 2, 2016 (Armour and Rockoff 2016).

examining the data generated by the US Senate finance committee investigation into Gilead.⁴⁵ Rather, what I found most interesting was *the absence of an overt criminal explanation* and rather the ostensible *presence of a multi-layered and contested social process* requiring the tools of sociological and political economy analysis.

The second reason for selecting this case, beyond fulfilling my two core ‘operational criteria’ - the pricing over *sofosbuvir*-based treatments ‘looms large’, meaning novel research findings have the potential of making important contributions to the debate over hepatitis C and potentially the broader discussions over pharmaceutical pricing and innovation. The medicines reflected not only a clinical marvel, but also the most profitable drug launch in pharmaceutical history. They became the subject of political, policy, and academic debates. In the arena of politics, they were raised by candidate Clinton on the campaign trail (DuVall 2016) and galvanized a US Senate investigation (Loftus 2015). In space of policy discussions, health agencies from around the world, policy institutes, and think tanks have wondered about how to interpret and respond to the challenge of hepatitis C medicines and drug affordability (Chahal et al. 2015; Reinhardt 2015; J. Walker 2015; Ward and Mermin 2015). At the sole forum on drug pricing organized by the Obama administration, *sofosbuvir* was cited as a paradigmatic of the drug affordability problems challenging many health systems (Pear 2015; US Health and Human Services 2015). Scholarly analysis of the pharmaceutical sector, ranging from medicine to industrial and health economics, has weighed in on the issues raised by *sofosbuvir* as well (Brennan and Shrank 2014; Chahal et al. 2016; Kesselheim et al. 2016; Leidner et al. 2015). Yet these analyses typically have obscured the innovation process behind *sofosbuvir*, thereby only providing partial explanations. A more complete explanation would be a boon for this disputed domain: given the large numbers of hepatitis C patients, but also the potential for breakthroughs in other disease areas with sizeable patient populations such as Alzheimer’s and certain cancers, the hepatitis C and *sofosbuvir* innovation process holds potential for pivotal lessons that will be closely examined by multiple stakeholders.

Third, the case of *sofosbuvir*-based treatments offers what Stake (2005:451) frames as an “opportunity to learn”, which in this case comes in two forms: its unique features as well as the practical access to data. The case of *sofosbuvir* may be considered to be an outlier by some analysts, based on the large numbers of patients with an infectious disease in hepatitis C as well as

⁴⁵ Interview 25

the curative and time-bounded nature of *sofosbuvir*-based treatments (Flier 2017). Indeed, many medicines with high prices are for diseases with smaller populations, and many of these medicines require long-term or even life-long treatment (Kesselheim et al. 2016; Montazerhodjat, Weinstock, and Lo 2016). However, as Stake (2005:451) has noted, “some times it is better to learn a lot from an atypical case than little from a seemingly typical case”. To heed Stake’s advice, I take inspiration from Mauss (1985:10), who noted that such cases possess “an excessiveness which allows us better to perceive the facts than in those places where, although no less essential, they still remain small-scale and involuted.” Indeed, the tensions that *sofosbuvir*’s pricing created for health systems - and the debates this instigated - were an important reason for why a large array of evidence became available for analysis over time. For example, the appendices in the US Senate investigation provided approximately 1,500 pages of internal corporate documents with detailed information on the valuation of *sofosbuvir* by Pharmasset, Gilead’s acquisition of Pharmasset, and their subsequent pricing of their treatment regimens. Interviews would not have yielded such detailed internal information about business strategies. Given the timeliness of the drug’s approval with the start of my PhD, I was also able to follow a slew of media accounts, new journal articles, and in-person events through which I could identify potential interviewees and gather more data. The case thus offered rare opportunities to gain access to sources of data pivotal towards answering research questions on drug pricing and innovation.

In sum, the innovation process behind *sofosbuvir*-based treatments possessed three compelling reasons to motivate my investigation: key operational criteria as a high and contested price for a breakthrough drug, a case which looms large over debates on the issues I am interested in, and finally an opportunity to learn with uncommon availability of data. Armed with an intriguing case, I set out to collect data that could answer the questions posed in this dissertation.

2.2 Data sources and collection

I drew on four sources of data – documents, semi-structured interviews, databases, and observation at meetings – to build the case study account.⁴⁶ I describe my data collection and analysis occurring over four phases as highlighted in Table 2.1, with the data collection all

⁴⁶ I also spent 10 clinic sessions with hepatitis C patients to better understand the clinical and treatment issues at stake. This time was split between a clinic in Los Angeles and Addenbrookes hospital in Cambridge, UK. Though I did not glean any direct evidence for the case study of the innovation process – individual patient cases were not part of my data set – as a future physician-social scientist, this time with patients provided helpful context and understanding in pursuing my research.

happening in the first three phases. A more detailed listing of the data including interviews is provided in Appendix A. In Phase I, I began with documentary evidence to build a starting foundation of understanding with which to gather further documentary data, identify and pursue interviews, and attend relevant meetings. Phase II mixed pursuits for all three sources of data, with phase III returning to a focus on documentary content. I periodically analyzed this data across all four phases of data collection in a manner described in section 2

Figure 2.2 Data collection and analysis across research timeline

		Phase I Nov 2014-March 2015	Phase II March 2015 - December 2015	Phase III Jan 2016 - September 2016	Phase IV Oct 2016 - April 2017
data collection	documentary content				
	semi- structured interviews				
	observation at meetings				
	databases				
data analysis					
		LEGEND=	not part of workflow	periodic focus	sustained attention

I bounded my data collection from these four sources based on the parameters and definitions outlined in the prior section in ways that I specify below for each data source. The four sources of data worked together, as I triangulated across them to assess the validity of the evidence. Documentary sources provided a significant portion of the evidence, given the wealth of available information in medical and policy journals, media accounts, and public databases. Pairing this with internal corporate documents and evidence, such as those offered in the US Senate investigation and interviews, allowed me to represent the innovation process.

Semi-structured interviews served two important roles: they provided narrative “thickness” to the drug development process by providing contextual information not presented at meetings or available in documentary sources that I had collected to that point. On several occasions, interviewees pointed to a development of which I had been unaware; they not only

provided their perspective and narration on the development, but also referred me to articles which could provide more evidence to interpret. The interviews thus “filled in” gaps and provided glue to many of the steps described in the innovation process. Second, they allowed me to check the relative significance of certain events and mechanisms that had emerged from documentary sources and observations at meetings. For example, I was able to understand the comparative importance of a certain technological advance or a public initiative from multiple experts within the field, rather than rely solely on an organizational document or journal article.

I used databases principally to gather financial data on the two key companies involved, Pharmasset and Gilead, as well as funding data on NIH projects. These numbers proved crucial to interpreting the risks and rewards taken by these organizations across the innovation process.

Finally, observations at meetings provided an opportunity to learn more about the strategic orientations of different actors, especially with regards to the deployment of hepatitis C medicines. Perhaps most crucially, they provided the chance to request interviews - several of my key informants emerged from in-person encounters at meetings or conferences. In the section that follows, I review my data collection methods for each of the sources.

Table 2.2 Data sources and collection methods

Data Source	Collection Methods
Documentary Sources	<ul style="list-style-type: none"> ○ Scientific and medical journals: I used Web of Science and a search of pivotal medical journals to identify key articles that covered scientific/therapeutic and policy developments. ○ Media accounts: I used Lexis Nexis to search for media accounts from 2000-2016, and also tracked news stories as they appeared based on real-time developments as well as snowballing. I focused on New York Times, Bloomberg, Financial Times, Wall Street Journal, STAT Health, and FiercePharma, as these are critical sources of news and reporting on the pharmaceutical sector and health care. I chose the 2000-2016 time frame based on my reading of scientific and medical journals, which indicated that this was the most active period for hepatitis C drug development. ○ Organizational/institutional reports: I searched websites for key organizations identified in other documentary sources (such as the NIH) and SEC filings for Pharmasset and Gilead. I reviewed earnings call transcripts between Gilead and investment analysts (gathered through S&P Capital database) as well as investor notes (gathered through Thomson Reuters). ○ Historical policy research: I searched for key papers and book chapters that documented the policy, legislation, and regulations that may have played a significant role in shaping the <i>sofosbuvir</i> innovation process. ○ The US Senate investigation released in December, 2015 was the most significant documentary source, providing over 1,500 pages of internal corporate documents for review.

Semi-structured interviews	<ul style="list-style-type: none"> ○ 41 interviews with initial sampling of 15 based on initial document review, and then snowball sampling to find the rest ○ State actors: National Institutes of Health scientists, publicly-funded university scientists, public health system officials (i.e. Medicaid) ○ Business actors: scientists at start-ups, biotech executives, senior leadership at large pharmaceutical companies, scientists at established companies ○ Financial actors: venture capitalists, investment analysts ○ *I also interviewed actors who did not neatly fit into one of these categories, but had expert knowledge on a relevant domain. For example, I interviewed several patient advocates who had kept close track of the drug development pipeline for over a decade as part of their formal organizational roles in treatment advocacy groups and provided detailed accounts of specific compounds and business strategies.
Databases	<ul style="list-style-type: none"> ○ S&P Capital for Gilead and Pharmasset's financial data, with statements in all recorded years and then analyzed for relevant data; I also was able to retrieve earnings call transcripts that I count towards my documentary sources. ○ NIH Reporter database for funding on publicly funded research related to the innovation process. ○ Center for Medicare and Medicaid Services drug spending database for financial data on what US public systems spent on <i>sofosbuvir</i>-based medicines. ○ I used the Wayback Machine, an internet archive, to examine the old webpages of two key companies in the innovation process that no longer operate in hepatitis C: Apath and Pharmasset. ○ OpenSecrets database provided political lobbying data on Gilead in Washington DC, which helped contextualize state-business relations with regards to drug pricing
Observation at meetings	<ul style="list-style-type: none"> ○ I gathered invitations to a total of 6 in-person fora of key actors related to <i>sofosbuvir</i> and also watched 3 such events online for a total of 9 meetings.

2.2.1 Documentary sources

Among documentary sources, I reviewed scientific and medical journals, media accounts, institutional filings and reports, and historical research.⁴⁷ I began with the scientific and medical literature in order to develop a firm understanding of the scientific and technical underpinnings of the hepatitis C and *sofosbuvir* innovation process. To develop my initial sample of this literature, I used two strategies: broad searches in Web of Science and PubMed as well as journal-specific queries. In Appendix A, I describe these searches in greater detail, as well as provide examples of the literature I reviewed.

The second documentary source was media accounts, which involved gathering key news stories of hepatitis C science and drug development. I used Lexis Nexis to search for relevant articles from January 1, 2010 to October 1, 2014, as this time frame allowed me to capture much of the drug development process into the post-approval stages. I searched through the news stories

⁴⁷ Here, I provide the general strategies I used for documentary sources. Refer to Appendix A for further detail and examples of the documentary evidence.

to identify ones that related to organizations involved in the *sofosbuvir* innovation process. One of the exciting challenges of my project: new stories on hepatitis C were written almost every week during 2014 and 2015. This meant that I needed to keep up with the rapidly evolving context and news events and be open to multiple news sources reporting on the case. Two online news sites dedicated to reporting on the industry - FiercePharma and FierceBiotech - as well as a health related news site, STAT Health, provided this more real-time reporting and analysis. I later did a second search in Lexis Nexis, from October 2, 2014 to December 1, 2016 in order to capture any further news articles that I might have missed in the intervening period since my initial search.

For my third documentary source, I compiled content across the organizations that emerged from scientific and medical journals as well as media accounts. For example, I used multiple NIH websites to download their plans for hepatitis C science, with the earliest document from 1999, with a NIH Action Plan for Liver Disease Research launched in 2003 with three annual follow-up updates to 2006. I also used SEC's online EDGAR filing system to search for all the quarterly and annual reports for the two main businesses at the heart of the development of *sofosbuvir*, Pharmasset and Gilead. These SEC filings contain extensive historical information on each of the businesses, their drug pipelines, and financial data. I reviewed the publicly available FDA documents on the approval of *sofosbuvir* to identify the key clinical trials (and their sponsors) used to evaluate the medicines. With this initial sampling of data from journals, media accounts, and organizational documents, I began to perform interviews, which I describe further below.

As the research unfolded and I had a better sense for the key political-economic dynamics at stake in the innovation process, I conducted historical research into policy, legislation and regulation that may have shaped those political-economic dynamics. For example, how was publicly funded science used in the innovation process? How did particular kinds of financing emerge? What were the rules, if any, around the distribution of capital by senior executives or pricing new medicines? I did not perform an exhaustive review of *all* such policies related to the pharmaceutical sector or biomedical innovation, as this would be beyond the scope of my dissertation project, but attempted to trace each of the important policy domains that may have been factors in the *sofosbuvir* innovation process. I performed internet searches to identify academic papers and book chapters that could offer this historical understanding. As examples: I leaned on studies by Block and Keller on public funding for commercialization, Gompers on the emergence of venture capital, Lazonick on the rules for share buybacks, and Kesselheim as well as

Rai and Eisenberg on US federal policies on property rules on publicly funded science (Gompers 1994; Keller and Block 2013; Kesselheim 2011; Lazonick 2015; Rai and Eisenberg 2003).

As I performed more interviews and better appreciated the role of the financial sector on the drug development process, I also reviewed earnings call transcripts between Gilead's senior executives and investment analysts on Wall Street, dating from Q3 of 2011 (just before Gilead announced its acquisition of Pharmasset) to Q3 of 2015 (16 reports). Additionally, I studied 11 notes from investment analysts assigned to the hepatitis C 'market', drawing on my access to Judge Business School's 'Thomson Reuters' database of investor reports.

Lastly, I was aided by the 18-month bipartisan investigation by the U.S. Senate Finance Committee (led by Senators Ron Wyden and Chuck Grassley). In a 144-page report with over 1500 pages in appendices released on December 1, 2015, the Senate Finance committee investigators chronicled Gilead's approach to pricing in detail based on approximately 20,000 internal documents provided by Gilead to the Senate Finance committee (United States Senate, Committee on Finance 2015). The Appendices of the US Senate report were of particular interest to me, as they contained meetings minutes from both Pharmasset and Gilead's board of directors, in addition to internal corporate strategy towards hepatitis C drug development and pricing, with some documents dating back to the late 1990s.

2.2.2 Semi-structured interviews

From my initial review of documents, I developed a starting sample of the key organizations involved in hepatitis C science, drug development and pricing — these centered on the state, business, and financial actors.

From this 'organizational layer', I identified key names and contact details via organizational websites and via attendance at meetings and conferences and subsequently emailed them with interview requests. After an initial wave of 15 interviews, I used snowball sampling to gather more names for potential interviews, eventually completing 41 total interviews. I tapered and eventually ended the process when I reached a point of empirical exhaustion for the purpose of answering my two research questions - after I had gathered all my key documents and had performed enough interviews where the key patterns had already emerged and been sustained both across the interviews as well as other data sources (Auerbach 2003). I approached my interviewees via two methods: direct emails and in-person encounters with an email follow-up. I usually asked for only 20-30 minutes of time, especially with senior

business officials, but was often granted more time when the interview actually began and unfolded.

I prepared a general set of questions, and adjusted them based on the person I was interviewing as well as the flow of the interview itself. I drew on best practices from semi-structured and elite interviewing, given the exploratory nature of my research into the innovation process as well as the kind of elite actors I aimed to interview (Berry 2003; Kincaid and Bright 1957; Peabody et al. 2013). Where a structured interview is composed of a carefully designed and fixed set of interview questions aimed at identifying common or divergent patterns across interviewees, a semi-structured interview allowed me the opportunity for probing by enabling the interviewee to expand freely on a given topic or question (Peabody et al. 2013). My questions aimed at four general areas, with specific probes adjusted to the particular interviewee. I usually began by asking a personal, open-ended question about their involvement and background in hepatitis C and/or pharmaceuticals. The middle part of my interview centered on unpacking the key actions they took and processes of which they were a part, and identifying their relationships with other key actors. I encouraged interviews to begin at the beginning and work forward in order to gain a historical perspective from their vantage. (i.e. telling the evolution of hepatitis C science from their vantage, or involvement in an acquisition process for a compound). I typically ended by asking the interviewee on their perceptions of the controversies around hepatitis C medicine and their pricing, and directions for further resources, questions, and interview contacts.

Given the controversial nature of hepatitis C medicines and the significant media attention on the topic, I aimed to put my interviewees at ease: rather than “interview you”, I aimed to “talk with you” and reminded respondents that their answers would be confidential (Berry 2003).⁴⁸ This approach worked, with only one publicly funded scientist and one hedge fund trader declining my interview request. I usually performed interviews that extended to 45-60 minutes long. Several key informants gave longer interviews and provided critical depth via their proximity to an important process or episode (usually over an hour). Throughout the interviews, I

⁴⁸ I followed the advice shared by Berry (2003:679) which had been passed on by a mentor, Robert Peabody: “None was more important than this: the best interviewer is not one who writes the best questions. Rather, excellent interviewers are excellent conversationalists. They make interviews seem like a good talk among old friends. He didn’t carry a printed set of questions in front of him to consult as the interview progressed; yet he always knew where he was going and never lost control of the discussion. He gave his subjects a lot of license to roam but would occasionally corral them back if the discussion went too far astray.”

made on the spot modifications to explore un-anticipated yet promising threads that emerged from the discussion (Kincaid and Bright 1957; Peabody et al. 2013). In order to maximize candor with interviewees and reveal potentially sensitive details of their activity, I did not perform tape-recordings and instead took notes by hand and wrote them up following the interviews (Berry 2003; Peabody et al. 2013). I was able to maintain my eye contact by only jotting down notes rather than entire passages. In almost every case, I immediately followed the interview by typing up my recollection of the encounter and waited six hours at the most in a small number of interviews.

2.2.3 Databases

In total, I used five databases to gather financial and spending data relevant to the case. First, for Pharmasset and Gilead, I used the S&P Capital database, which contained all the financial statements for the companies over their recorded history. Second, to account for US public investments in science, I used the NIH's REPORTER database to identify grants to particular labs, including private labs at companies such as Pharmasset. Third, I used an archival database called the *Wayback Machine* - a digital archive of the Internet - to find Pharmasset and Apath's original website pages in order to generate the early history of the biotechnology companies and their sources of funding. The fourth database I used was the Center for Medicare and Medicaid drug spending database, which tracks public sector spending on pharmaceuticals by the two major public programs in the US: Medicare and Medicaid. This enabled me to understand the impact of *sofosbuvir* in terms of overall budgetary expense and treatment access. Fifth and finally, I used OpenSecrets, a database that tracks spending on political lobbying in Washington D.C. by different special interests. I searched for Gilead's lobbying spending as a way into understanding how the state-business relationship evolved with the company's hepatitis C pricing strategy.

2.2.4 Observation at meetings

From December 2014 to January 2016, I attended 6 major meetings related to hepatitis C medicines and I also watched proceedings of 3 meetings via virtual recording. All of the meetings brought together multiple actors of interest to my research question, with the major difference being the 'lead convener': sometimes it was a different branch of government (such as the FDA or the CDC) or industry (such as Gilead or a Gilead-funded academic institute) or clinicians (such as

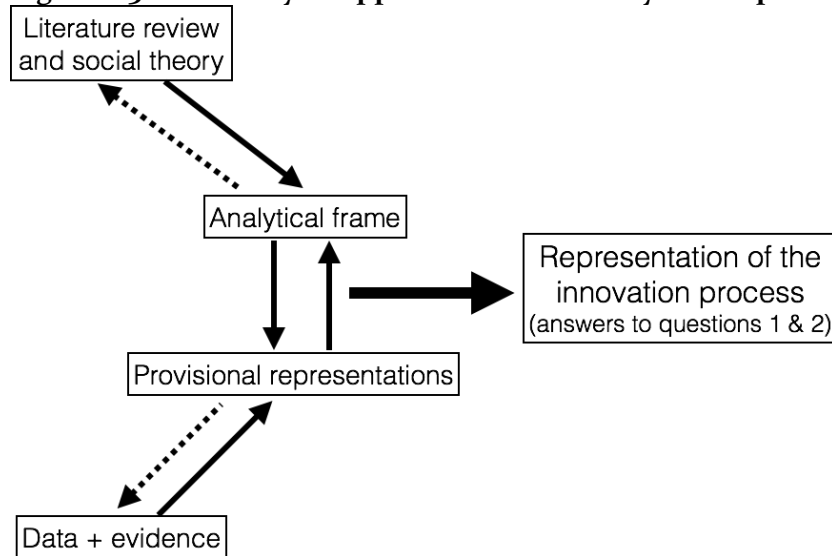
the British Association for the Study of the Liver - BASL). The only major actor absent in most of these meetings were investment analysts and other Wall Street and London financial actors; I used the transcripts of earnings call as well as investor notes as key sources to understand their vantage. For each of the meetings I attended in-person, I actively jotted notes and composed a field note in the evening (Emerson et al. 2011). For each of the meetings I observed virtually, I had the freedom to rewind and listen, and I similarly jotted down key quotes and later composed notes.

2.3 Data interpretation and analysis

I adapted elements of Ragin's constructivist approach to social science research (see Figure 3.2) in my approach to data analysis, which calls for an iterative approach to building a case study (Ragin 1994). I alternated between analyzing data across my three sources to build provisional representations of the innovation process (via research memos and papers) and drawing on sociological and political economy literatures to conceptualize the analytical frame through which I was interpreting these provisional representations. By analytical frame, I refer to the literatures and concepts described in chapter 1 which provided tentative lenses through which to initiate my exploration but which shifted and evolved through the research process.⁴⁹ I brought these analytic frames into juxtaposition with the representations of the innovation process yielded by the data and evidence I had collected in order to identify gaps, continuities, and tension points. These juxtapositions either encouraged me to either gather more data (i.e. when an analytical concept revealed gaps in my current data collection) *or* review the sociological and political economy literatures (i.e. when a piece of evidence could not be explained by the existing analytic frame I had been using at the time). As represented in Figure 2.2, this iterative approach between my data and my analytical resources allowed for a progressive approach to building a valid representation of the case study.

⁴⁹ For more on these analytical frames, see Chapter 1 and the sections devoted to the entrepreneurial state, financialization, and capital as power.

Figure 2.3 Data analysis approach to case study development



Source: Adapted from Ragin (1994), *Constructing Social Research*

This representation amounted to a sociological ‘account’ of the innovation process behind *sofosbuvir*-based treatments. Much like a clinician combining a patient history with quantitative data from diagnostic tests to make a clinical diagnosis, I take ‘account’ as a double-entendre à la Stark (2000): both a set of *numbers* (such as costs of drug development, revenues, patients treated), as well as a *narrative* of the innovation process.⁵⁰ Each gave the other context – whereas *numbers* enabled a quantitative picture for risks and rewards, *narrative* detailed the nature and significance of social processes that could help make sense of those quantitative metrics. Through the combination of numbers and narrative in a clinical account of the innovation process, I could make a sociological and political economy diagnosis of the mechanisms that produced Gilead’s pricing and yielded a particular set of innovation and public health outcomes.

The data analysis itself fell largely into two modes of work. First, I built a detailed historical record of the innovation process. This record was a ‘live’ document which I updated throughout my data collection process and drew from all three sources of data. Second, I tracked key financial figures across the innovation process from documents as well as the S&P Capital and NIH databases, in keeping with my aim of not only capturing the *narrative* but also the *numbers*

⁵⁰ Stark (2000:5) captures the intertwined nature of narrative and numbers: “Etymologically rich, the term ‘account’ simultaneously connotes bookkeeping and narration. Both dimensions entail evaluative judgments, and each implies the other: Accountants prepare story lines according to established formulae, and in the accountings of a good storyteller we know what counts. In everyday life, we are all bookkeepers and storytellers. We keep accounts and we give accounts.”

that composed the account. These financial figures included the costs of research and development for *sofosbuvir*, the funding and financing behind the innovation process from multiple public and private actors, the revenues accrued by Gilead for *sofosbuvir*, as well as the distribution of these financial flows to shareholders and senior leadership. I used a third strategy of analysis – qualitative coding – to a lesser degree. I only used coding on earnings call transcripts to identify the strategic interests communicated by investment analysts and Gilead’s senior leadership. However, I did not code my individual semi-structured interviews as I was not interpreting their ‘talk’ for discursive patterns but rather for key events, relationships with other actors, and elaborations of technological and political-economic processes. I tagged these data points as I reviewed my interview notes and integrated them into the emergent and provisional narrative.

To ensure greater validity, I subjected this narrative to two further methods: within-case triangulation and counter-factuals. Both approaches helped test provisional representations of the innovation process and refine the empirical chapters and argument laid forth. Within the case, I triangulated across accounts provided by different actors and documentary sources to reconcile discrepancies or gaps in the narrative (Stake 2005). I also compared key events and processes in the innovation process with other compounds and firms in the hepatitis C arena beyond Gilead and *sofosbuvir*: a key example was comparing acquisitions of hepatitis C assets by a number of large companies. Such comparisons helped test alternative mechanisms and understand the extent to which I was capturing the right political-economic dynamics rather than isolated events or viewpoints.

Additionally, I used counter-factual reasoning at specific points in the provisional narrative to challenge and sharpen my representation of the innovation process. Counterfactual reasoning involved posing alternative causal processes that could have occurred and run counter to the ones established via empirical research (Collier 2011; Fearon 2011; Levy 2009). As Levy (2009) puts it, “a theory that specifies the consequences of both X and not X tell us more about the empirical world than a theory that specifies only the consequences of X.” For example, my analysis of Gilead’s acquisition of Pharmasset is based on asking what might have happened to Pharmasset if it had attempted to remain a stand-alone company and if Gilead had not existed as an acquisition specialist capable of leveraging its significant capital. Posing the counterfactual strengthened my analysis of the mechanisms by which speculative financial markets and

shareholders of incumbent pharmaceutical companies like Gilead influence the trajectory of drug pricing.

I also used my provisional representations of the innovation process to garner feedback during my investigation. In one instance, the publication of a peer-reviewed article in the *British Medical Journal* in July, 2016 generated further feedback from two peer reviewers, BMJ's editors as well as written responses from Gilead Sciences and other scholars of pharmaceutical innovation (Roy and King 2016). Throughout the research, my supervisor, Dr. Lawrence King, as well as discussions with several peers researching pharmaceuticals also guided and improved my methodology and analysis. Additionally, I presented my research at several major conferences, including at the European Association for the Study of Science and Technology (EASST) in Barcelona (in September of 2016) and at the Harvard Medical School's MD/PhD conference in the social sciences and humanities, at which I was able to gain useful feedback.

By (1) alternating between my data and the analytic frame, (2) interpreting my data with provisional narrative-building and retrieval of key numbers, (3) performing within-case comparisons and counter-factuals, and (4) engaging in ongoing feedback and consultation with multiple colleagues and advisors, I produced an analytically valid representation of the hepatitis C innovation process from the data I collected.

2.4 Limitations in research design

Though I provide a more complete accounting for potential limitations of my research findings in chapter 7, two ex-ante limitations are important to anticipate and address.

The first potential limitation relates to my research into the role of the state. With regards to the state, I primarily focused on the role of innovative public sector organizations, such as the NIH, in contributing to the innovation process behind *sofosbuvir*. Unlike my research into an entrepreneurial state, my tracing of the relationships between other state actors and business and financial actors (state-finance, state-business) required me to lean on historical research done by others to understand the key policies, regulation, and legislation that shaped the rules by which specific political-economic dynamics may have unfolded as they did. By drawing on research by others, I may have missed important dynamics or erred in the interpretation of the ones I present. Where possible, I tried to study at least two different accounts (i.e. reading multiple histories of the Bayh-Dole Act, for example). Furthermore, my aim was not to perform

an exhaustive historical analysis of each of those rules, policies and legislations⁵¹, but rather trace the important shifts to the specifics of the *sofosbuvir* innovation process. In other words, this historical research provided critical context – but the foreground remained the innovation process behind *sofosbuvir*.

A second potential methodological limitation: my focus on a single, successful case of drug approval, *sofosbuvir* (and its combination therapies), at the exclusion of many other hepatitis C compounds that were pursued in the broader drug development process. Analysts of pharmaceutical innovation are right to point out that tens of compounds reached phase I and phase II trials for hepatitis C, with a small minority even reaching to phase III and FDA approval. I did not, however, perform an analysis of the trajectories of all potential hepatitis C compounds (both successful and failed) as well as all the business units that attempted to pursue therapies for the disease. One argument against my approach is that it would underplay the contributions of private businesses to the hepatitis C innovation process.

Such a critique, however, falls for the same traps laid by the ‘risk’ argument, in which summing the private industry contributions is argued to reflect Gilead’s prices (Calcoen et al. 2015).⁵² My approach sought to develop an alternative to this debate through a thick description of a single compound’s trajectory, a method that could not be used to trace all or even multiple potential compounds within the context of a PhD time frame.

But my approach also mitigated against this potential critique in three ways. First, my accounting of the upstream stages of hepatitis C research was historically deep, and these early stages of discovery apply to *all* onwards drug development – indeed, as we will see, any drug development rested on these contributions. This historical retrieval of the early science anchored my broader analysis of the innovation process. Second, my approach included not just a product-level view of *sofosbuvir* but also a business-level, organizational view: I therefore present the costs of *all* research and development attempted by the businesses that developed *sofosbuvir*, which includes the costs of all failed compounds. Third, I bring in an industry-level view at critical junctures of the innovation process by tracing the relationships between developers of *sofosbuvir*

⁵¹ As I indicate in chapter 6, this would be a separate project, and might draw on the model set by Gretta Krippner’s (2011) work on tracing the relationship of the state with financialization in order to develop deeper insights into the role of the state in the financialization of biomedical innovation.

⁵² A study funded by Gilead Sciences and performed by Boston Consulting Group aimed to make this argument, showing an overall 2% success rate by the industry in getting hepatitis C compounds all the way to approval (Calcoen et al. 2015).

and competing business organizations. Two examples capture this vantage: I juxtaposed the *sofosbuvir* valuation with the prices of the key prior therapy for hepatitis C, *interferon*, and I also captured the trajectory of two other hepatitis C compounds and competing businesses (Bristol Myers Squibb and Merck) to indicate the ‘gold rush’ dynamics of drug development. By taking these steps, I gave readers insight into the broader industry-level dynamics shaping the innovation process.

Any innovation process for a therapeutic area like hepatitis C contains a multitude of scientific, technological, and business events, some of which may fall from view during research. But the guidance of sociologist Charles Tilly (1990:36) offers a way through the paralysis that may otherwise set in from studying a seemingly infinite territory, in that he recognized the role of the researcher as “not to give a ‘complete account’ (whatever that might be), but to get the main connections right”. While my case focuses on those most relevant to *sofosbuvir*, the parameters I set in section 3.1 (regarding innovation process and relational dynamics) allowed me to trace outwards to capture those connections most crucial in answering my research questions. These connections, I argue, can be used to make sense of the multiple dimensions of the *sofosbuvir* innovation process, and illustrate the dynamics that influence the prices of new medicines.

2.5 Summary of research design

My research design employs a single case study to answer the two central research questions. I defined the central object of study to be the *innovation process* behind *sofosbuvir*-based treatments and the *relationships* between multiple organizational actors and political-economic mechanisms that can explain *sofosbuvir*’s pricing as well as the outcomes of the process (risk-reward nexus, public health outcomes). By drawing on four sources of data – documentary content, semi-structured interviews, databases, and observation at meetings – and then engaging in an iterative process of analysis, I built a valid representation of the case study. The products of this data collection and analysis are shared in the three empirical chapters that follow. The three chapters unfold in largely a historical manner, begin with the early stages of science and research behind hepatitis C and moving forward into drug discovery, development, and deployment.

Chapter 3. Making the Invisible Visible: The Hands of an Entrepreneurial State and a Shadow Epidemic

*"Oh GREAT LIVER in the sky,
Show us where and tell us why
Send us thoughts that will inspire us
Let us see this elusive virus
If we don't publish soon,
They're going to fire us!"*

- Dr. Harvey Alter, Chief, Infectious Diseases Section, National Institutes of Health,
Excerpted poem regarding NIH's pursuit of the hepatitis C virus from Alter (2013)

Decades long public backing, beginning in the 1960s, allowed for both the unveiling of a virus with a long, chronic course of pathology and illness and for the technologies necessary for developing its antidote. Over this period, a network of public institutions and funding turned a shadow epidemic into a tractable target for intervention and a magnet for further financial investment. This first empirical chapter chronicles this story, centering on the ascent of an entrepreneurial U.S. state in the pursuit of understanding a virus and plotting its demise. I begin with a focus on tracing the early stages of scientific discovery and technological development and trace them forward into subsequent steps in the drug development process. As I follow the transformation of a shadow epidemic into a tractable target for biomedical intervention, I draw on Mazzucato's (2013b) concept of an entrepreneurial state to illuminate its critical role *across multiple stages of the innovation process*. The description of this process draws on scientific and medical journal articles, interviews with scientists, as well as public database queries of research grants, and is summarized in Table 3.1 below.

This entrepreneurial state manifested itself via three interdependent threads over four decades: the provision of patient investment across the upstream-downstream terrain of the innovation process, risk-taking capital at technological frontiers that created new possibilities for drug development, and the legal contract and apparatus for converting public knowledge into private assets and organizations.⁵³ This patient investment, risk-taking, and deal-making by an entrepreneurial state set private capital in motion for hepatitis C drug development and also shaped the direction of the innovation process towards a curative therapy. Yet the state's deal on

⁵³ The temporal unfolding of knowledge regarding hepatitis C – from a matter of post-war curiosity to contemporary concern – gives us the opportunity to map the parallel emergence and evolving roles of public organizations in the innovation process during the 20th century.

the conversion of public into private intangible assets became one of the key factors in the financialization of hepatitis C drug development, as it bolstered the conditions for a particular mobilization of speculative capitals in financial markets of intangible assets.⁵⁴

First, in section 3.1, I follow the emergence of the National Institutes of Health, with a central group of scientists in Bethesda, MD, along with scientists at other government agencies and the private company Chiron, in leading efforts to elucidate viral hepatitis and identify the infectious pathogen behind its chronic form. A signature effort begun by NIH scientists in the late 1960s comprised of tracking patients over the course of decades to understand the “natural history” of the disease. These long-term studies of patients with liver inflammation formed the basis of grasping hepatitis C not as a benign disease, but as a matter for both individual concern and as a population health problem of epidemic proportions. This clinical and epidemiological visibility provided the foundation for further investment in therapeutic development that led to *sofosbuvir*.

Second, public investments and research (section 3.2) into overcoming technological barriers hindering hepatitis C drug development in the 1990s led to a critical breakthrough – the *sub-genomic replicon* – that “dynamized in” private capital from small and large pharmaceutical companies.⁵⁵ With the discovery of the replicon, the state went beyond cultivating the seedbed of basic science and proactively took a radical risk in extending the technological horizon upon which drug development could occur.

Third, the state continued this orientation towards risk-taking into therapeutic development, supporting the development of ‘nucleoside science’ – a kind of medicinal chemistry used for its anti-viral properties but shunned through the 1980s into the 2000s by large companies for the risks posed by nucleosides in clinical trials (section 3.3). This research into nucleoside science, led by chemist Ray Schinazi based at the Veterans Affairs hospital and Emory University, also led to a new company in 1998, Pharmasset, that would ultimately develop the curative backbone, *sofosbuvir*, over the subsequent decade. The state created the legal and organizational apparatus with a series of regulatory shifts in the 1980s, exemplified by the 1980 Bayh-Dole Act, by

⁵⁴ While I foreshadow this dynamic at the end of this chapter, I use chapter 5 to more fully unpack this mobilization.

⁵⁵ This contrasts with the typical role assigned to the state in economic debates, in which public investments are said to ‘crowd out’ private capital. Here we observe the opposite to be true: investments in the replicon created a market for hepatitis C drug development which private capital attempted to exploit as an economic opportunity (Mazzucato 2016).

which publicly funded knowledge on nucleoside science could be converted into privately owned intangible assets to launch Pharmasset. I highlight the “triple helix” of publicly funded science, university labs, and small enterprises enabled by the Bayh-Dole Act, and point towards its consequences for both the financialization of drug development as well as the distribution of risks and rewards in the innovation process.

Table 3.1 The Entrepreneurial State behind hepatitis C and *sofosbuvir*

Phase of contribution (and relative timeline)	Description and significance	Actors	Key papers and/or reported funding
Identifying the virus			
Identifying NANBH (early 1960s – 1975)	Process of elimination by NIH scientists led to discovery of a ‘non-A, non-B’ hepatitis pathogen	NIH Blood Bank program	Feinstone et al (1975)
Confirming causative viral pathogen (1975-1989)	Scientists continued to test possible viruses to identify pathogen causing viral hepatitis	NIH, FDA, CDC	Alter et al (1978b), Tabor et al (1978a) Bradley (1979)
Molecular biology techniques used to discover causative pathogen (1985-1989)	Scientists manipulated and cloned DNA through new genetic engineering tools, leading to new screening techniques that led to hepatitis C discovery	NIH, CDC with Chiron	Choo et al (1989)
Tracking the virus			
Long-term tracking studies (early 1960s to present)	Patients receiving transfused blood with hepatitis C tracked over four decades to reveal significant patient and public health consequences	NIH intramural studies, VA, CDC, Armed Forces Institute of Pathology	Berman et al (1979), Ishak et al (1995), DiBisceglie et al (1991), Seeff (1992), Alter (1992)
Research tools for drug development			
Replicon development (1995-2002)	German and US scientists created a research tool called the replicon that enabled replication of the parts of the hepatitis C virus with out which drug development could not proceed	Germany government (German Research Society, Ministry for Education and Research); NIH extramural awards	Lohmann et al (1999a) and Blight (2000) \$3.4 million for Rice lab to develop replicon; \$10.76 million total for hepatitis C research; German research funding from mid-1990s not publicly listed
Replicon commercialization (2000-2003)	Replicon was manufactured and distributed by Apath, a company supported through multiple major NIH grants, in order to enable hepatitis C drug development across company labs	Small Business and Innovation Research Programme	\$1.81 million for replicon commercialization; \$9.39 total to Apath from NIH and NIH SBIR
Medicinal chemistry for drug development			

Nucleoside science (1991-2005)	Provided funding and support for anti-viral development that would form basis for Pharmasset	NIH, VA	\$2.72 million for viral hepatitis research; \$8.84 million total from NIH; VA spending not reported
Pharmasset launch (1998-2004)	Multiple early stage grants provided important financial support and market signal to venture capitalists	Small Business and Innovation Research Programme, VA, Emory	\$1.01 million for hepatitis C; 2.46 million total from NIH SBIR; VA spending not reported
CONTRIBUTIONS BELOW WILL BE DETAILED IN CHAPTER FIVE			
Sofosbuvir discovery (2005-2007)	McGuigan method used by Pharmasset to develop <i>sofosbuvir</i>	British Medical Research Council, European Research Council, Belgian government	Funding not reported by MRC; research performed in mid-1990s McGuigan et al (1996a)
Clinical trials			
Phase II clinical trial (2011-2013)	NIH-led study tested sofosbuvir in vulnerable, high-risk populations	NIH	Estimated to be ~\$14.2 million to run anti-infective trial in Phase II Osinusi et al (2013b)
Pharmasset grant for clinical development (2010)	ACA grant provided to Pharmasset to perform clinical trials	Internal Revenue Service (IRS) and Health and Human Services (HHS)	\$244K grant from Affordable Care Act ('Obamacare') provision ((United States Senate, Committee on Finance 2015:13)

*See Appendix B for further details on NIH funding sources, all of which were identified using the NIH Reporter database

3.1 Discovering Hepatitis: From the Front Lines of War to the National Institutes of Health

The greenish hue creeping over human skin, termed *jaundice*, drew the eyes of medical scholars since antiquity (Gardner and Paul 1958; Rosner 2002). Episodes of war accompanied outbreaks of this condition, but the precise causes – beyond the suspected inflammation of the liver, termed *hepatitis* – remained a mystery (Gardner and Paul 1958).⁵⁶ Investigating hepatitis in the twentieth century also began in the crucible of war. In World War II, 200,000 American soldiers suffered from hepatitis, marking the pathology as a matter of prime importance to military researchers (Gardner and Paul 1958). From their analysis of patient cases and samples, doctors suspected two infectious routes for this hepatitis: one via the blood, and the other oral-fecal (Zimmerman et al. 1947).⁵⁷ Yet the precise pathogens that traveled along these routes and their pathological consequences for patients persisted in obscurity. Four decades of research centered at the National Institutes of Health as well as other key public agencies lifted the veil.

3.1.1 A home for viral hepatitis research: the emergence of the National Institutes of Health

The process of ‘following’ viral hepatitis in the post-war period fell largely to an unlikely group of collaborators at the National Institutes of Health (NIH) campus in Bethesda, Maryland along with accompanying scientists at other government agencies.⁵⁸ With the study of liver diseases still in its infancy, investigation into hepatitis emerged from a network of scientists and clinicians that ranged in expertise from blood banking to infectious disease to hepatology.

Before World War II, US government support for scientific research was a fledgling but largely marginal area of focus. The passage of the Public Health Services Act of 1944, however, inaugurated a more intentional strategy to pursue scientific research in the national interest. Emerging from prior iterations of government laboratories, the National Institutes of Health grew rapidly in the post-war years: from a total budget of \$8 million in 1947 to \$1 billion in 1966

⁵⁶ The Babylonian Talmud of the 5th century BC referred to “epidemic jaundice”. Through out the Middle Ages and into the American Civil War, Franco-Prussian War, and World War I, bouts of jaundice – some times termed “campaign jaundice” – befell soldiers (Gardner and Paul 1958; Rosner 2002).

⁵⁷ One of the researchers, Hyman Zimmerman, served as a doctor stationed in north-east France during the Battle of the Bulge and returned to the U.S. after the war to serve in the public Veterans Affairs system as a doctor and research scientist over the next four decades. He is considered the “father of hepatology”, the study of liver disease (Kennedy 1993).

⁵⁸ Interviews 17, 20, 23 provided insight to this period.

(Harden 2008; NIH 2017a). From an initial handful of centers between 1946 and 1949, the NIH grew to 15 Institutes by 1970 and 27 by 1998. These investments aimed to give the US an economic and national security edge in the Cold War (Slaughter and Rhoades 1996).⁵⁹ Over the decades following the war, several new Institutes as part of the broader NIH would serve as homes to viral hepatitis research (see Table 3.2): the Laboratory for Infectious Disease (LID) which later became part of the National Institutes for Infectious and Allergy Diseases (NIAID), the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute for Arthritis, Metabolism and Digestive Diseases (later renamed National Institutes for Diabetes and Digestive and Kidney Diseases – NIDDK). Scientists at these Institutes found their physical home at the NIH’s Bethesda, Maryland campus and formed what is known as the organization’s ‘intramural’ (or internal) research program.⁶⁰

The scientific pursuits in these Institutes and Centers were closely linked to patients and clinical care: as part of the Public Health Service Act of 1944, the NIH was authorized to conduct clinical research, which manifested in the form of a new research hospital called the Warren Grant Magnuson Clinical Center (often called simply the “Clinical Center”) at the Bethesda campus (Harden 2008). The Clinical Center served as hub for the growing campus, with the hospital opening in 1953 with 540 beds (Harden 2008). This hub, which continues to serve as the heart of the NIH campus, placed patients and research laboratories within close proximity to enable collaboration between doctors and lab scientists. The NIH budget, which stood at \$52 million in 1950, crossed \$1 billion by 1966 (NIH 2017a). Though the rate of increase in science funding slowed in the late 1960s and 1970s from health-related funding going to Medicare and Medicaid and concerns over high inflation, the rapid post-war growth provided an institutional

⁵⁹ In 1950, Franklin Delano Roosevelt’s director and founder of the Office of Scientific Research and Development, Vannevar Bush authored a seminal report, *Science: the Endless Frontier*, arguing that scientific knowledge would help determine the country’s health, economic opportunity, and national security. Bush (1945:8-9) wrote at the time, “The government should accept new responsibilities for promoting the flow of new scientific knowledge and the development of scientific talent in our youth. These responsibilities are the proper concern of the Government, for they vitally affect our health our jobs and our national security. [...] For many years the Government has wisely supported research in our agricultural colleges and be the benefits have been great. The time has come when such support should be extended to other fields.”

⁶⁰ The intramural program refers to the NIH’s internal research program at their Bethesda campus, which as of 2015 represents 10% of the organization’s overall budget ~\$32 billion budget. This contrasts with the ‘extramural’ program, in which 80% of NIH’s budget is granted to a broad network of research scientists based primarily at universities (NIH 2017a). We return to the extramural program later.

base for scientists interested in viral hepatitis to pursue an uncertain course of research (NIH 2017a).

Table 3.2 Main NIH Institutes involved in hepatitis C research

NIH Institute	Main hepatitis C contributions
National Institutes for Infectious and Allergy Diseases (NIAID), formerly the Laboratory for Infectious Disease	Unveiled life cycle of hepatitis C virus, collaborated with other institutes on clinical research and trials, later led a Phase II clinical trial for <i>sofosbuvir</i> (Alter et al. 1978a; Lindenbach and Rice 2013; Osinusi et al. 2013b)
National Heart, Lung, and Blood Institute (NHLBI); formerly the National Heart Institute	Tracked patients after blood transfusions for viral hepatitis and created first national strategy to screen blood for hepatitis C (Alter 2013; Alter and Houghton 2000)
National Institutes for Diabetes and Digestive and Kidney Diseases (NIDDK); formerly the National Institute for Arthritis, Metabolism and Digestive Diseases	Tracked long-term patients with viral hepatitis, pioneered initial treatments for hepatitis C with <i>interferon</i> , unfolded hepatitis C pathophysiology and outcomes (Hoofnagle 2004; Hoofnagle et al. 1986a)

3.1.2 *Heart of a viral hunt: tracking chronic infectious hepatitis*

Both the precise pathogens behind infectious hepatitis and their pathological consequences were revealed in part via *long-term tracking studies* led primarily by the National Institutes of Health along with accompanying studies by the Veterans Affairs administration and the Centers for Disease Control. Yet the circuitous route to understanding viral hepatitis did not pass through the liver, but instead via the perils of a new procedure: open heart surgery. Two years following the first open-heart surgery in Philadelphia in 1953, the NIH began performing them at their Clinical Center in Bethesda (Harden 2008). These surgeries often aimed to replace faltering heart valves, the tough windows of tissue that control the flow of blood through the organ. In early attempts, however, lengthy procedures with significant blood loss meant patients required large transfusions of blood. Beginning in the mid 1960s, with the knowledge that one form of viral hepatitis traveled through the blood, a group at the National Institutes of Health's Laboratory for Infectious Disease (LID) wondered about the contents of this transfused blood and the fate of the patients that received them (Alter 2013; Walker 2006). A handful had shown abnormalities related to the liver after the transfusion, but whether this was a pattern with clinical consequences was an open question. By taking a blood sample from patients prior to

surgery, and then following them in the subsequent months, they hoped to shine light on this potential cause and course of liver pathology (Walker 2006).⁶¹ This concern and curiosity, however, was not theirs alone.

Blood transfusion had only been used sporadically before World War II, but procedures like open-heart surgery required their use on a growing scale in the post-war years. This need led to a wide-scale development of blood banks and blood transfusion services, including at NIH's Clinical Center, with its Blood Bank Department (Walker 2006). The department became a pivotal hub for research into viral hepatitis, coordinating and leading studies to track viral hepatitis in patients following open-heart surgery (Alter 2013). Collaborating with the Laboratory for Infectious Disease, scientists found that a third of those receiving transfusions developed elevations in liver enzymes (Alter et al. 1975; Alter et al. 1978a).⁶² These elevations signaled the distress of liver cells, as they leaked enzymes into the blood. Though these patients did not experience symptoms or signs of a *clinical hepatitis* from liver failure (such as jaundice), this *biochemical hepatitis* yielded evidence of a liver coping against some attacking pathogen (Berman 1979).⁶³ Hiding from their observers, however, lurked not one, but *two* distinct pathogens. These studies enabled an elucidation of these pathogens, ultimately not only leading scientists towards hepatitis C but also revealing the clinical consequences of the pathogen behind the disease.

First, these long-term tracking studies allowed NIH researchers to test, by process of elimination, multiple potential pathogens that were suspected to be the cause of this infectious hepatitis. During the 1960s, scientists including Dr. Harvey Alter at the NIH had already identified one pathogen behind blood-borne hepatitis, which they had dubbed hepatitis B (Alter 1999). Over the next five decades, Alter would become a meticulous steward and investigator for the efforts

⁶¹ Dr. Purcell, an infectious disease doctor then at LID who would become a central figure in viral hepatitis in subsequent decades, describes the process in an oral history for the NIH: "So we set up a program whereby we would get a blood sample from patients who would be undergoing surgery, to take [a sample] Monday morning, [as they] came in for the week's surgery, get a blood sample from them, and then – if they survived the surgery, [which not all of them did] – follow them at weekly intervals for the first couple of months, and then at monthly intervals for six months, and then perhaps indefinitely after that. Bob (his collaborator) had an epidemiologic nurse, but either she or I or both of us would go over, or go out around about four states here, to the homes of these people – because they were generally too sick to come out" (Walker 2006:7).

⁶² Enzymes are proteins that catalyze chemical reactions; in this case, they were measured as an indicator (otherwise known as a biomarker) for a potential disease process.

⁶³ Biochemical hepatitis refers to a chemical or molecular change that is measured in the blood, whereas clinical hepatitis refers to a change that can be observed during a physical exam or biopsy of liver tissue, or experienced by a patient.

begun by scientists at the Laboratory for Infectious Disease and at the Blood Bank Department of the NIH (Alter 1999). One of Alter's first questions with his colleagues: did hepatitis B cause the transfusion-associated hepatitis in the patients they had tracked thus far? They found, surprisingly, that *only a third of those patients had been infected with this particular virus* (Alter and Houghton 2000; Alter, et al. 1978b). Two out of every three patients were thus infected with a mystery pathogen. They tested another suspect which had come to the fore: hepatitis A. In 1975, a group of scientists at the Laboratory for Infectious disease had used direct observation via electron microscopy to identify hepatitis A as a viral cause of hepatitis (Feinstone et al. 1975; Feinstone et al. 1973). But upon testing the non-B blood, they found that not a single case was related to Hepatitis A, which they knew to be instead transmitted via the fecal-oral route.

Publicly funded scientists had been pivotal to solving two central post-war puzzles of viral hepatitis: identifying the pathogens suspected to cause blood-borne (Hepatitis B) and fecal-oral (Hepatitis A) injury to the liver. But in solving these two puzzles, another had emerged: grappling with a third pathogen dubbed “non-A, non-B hepatitis”.⁶⁵ Alter, Purcell, and others who had worked on viral hepatitis redoubled their efforts, but their initial confidence of a quick resolution and identification of a “hepatitis C” withered (Alter 2013). Another fifteen years would pass with the virus remaining a ‘known unknown’, a story to which we return later.

Second, this NIH tracking study would be central to a broader public effort to understand the extent to which this pathogen posed a threat to patients and population health. At the time, elevated levels of liver enzyme (‘transaminitis’) had been the only notable change. But did patients have worse health or mortality outcomes? Little was known: the virus would remain invisible with out further study of its consequences (Alter and Houghton 2000). The only solution was to remain patient and follow the pathogen where it took patients and their bodies. In addition to the patients followed by Dr. Alter at the NIH Blood Bank, three other groups began to track the course of this pathogen: scientists at the Veterans Affairs administration and another NIH node, the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK), and the Centers for Disease Control (CDC) (Alter et al. 1975; Berman 1979; L. B. Seeff et al. 1987).

⁶⁵ Alter recalled the debate over naming this mystery pathogen: “We considered calling it hepatitis C at that time, but Purcell (Alter’s collaborator) insisted on the more amorphous term because we had not yet proven it was a virus and, if so, how many agents might be involved” (Alter 2013:9). He continued “We were also pretty confident that we would discover the NANB agents in a relatively short time and then apply the proper nomenclature. This was a confidence that was shattered over the next 15 years of intensive – but vain – effort” (Alter 2013:9).

Researchers at these public agencies speculated about the pathogen's consequences. One study published in 1975 and another in 1979 found that a majority of cases with non-A, non-B hepatitis led to persistent liver damage, with more serious scarring of liver tissue occurring in approximately one-fifth (Berman 1979). But crucially, patients did not experience symptoms, leading authors to continue to guess about the consequences of this pathogen. The authors suspected that the disease might resolve itself in many patients, suggesting, "in view of the generally asymptomatic nature of this disease and of the trend toward spontaneous biochemical resolution, it would be difficult to evaluate the efficacy of drug therapy" (Berman 1979:1). These researchers would rely on another set of biomedical tools from pathology in order to make a determination over the severity of the disease.

Because the pathogen caused its damage slowly, reports of organ failure or patient symptoms could not guide researchers (Ghany et al. 2008). Instead of these more observable measures of disease progression, researchers had to focus on molecular markers in the blood (called *biomarkers*, such as liver enzymes in blood samples) as well as changes in liver tissue acquired via biopsy samples (Bedossa and Poynard 1996). These measures could indicate both the *presence* and the *progression* of the disease course. Histologists at the Veterans Affairs administration and Armed Forces Institute for Pathology were among the leading analysts of such tissue (Ishak et al. 1995; Knodell et al. 1981). Drawing on studies from the late 1960s and 1970s, a group of doctors and pathologists across these two public institutions introduced the initial scoring system in 1981 which would later be iterated upon to arrive at the scoring system that has become popularized in clinical trials and treatment policy decisions (Bedossa and Poynard 1996; Ishak et al. 1995).⁶⁶

By applying these analytical tools to their cohorts of patients infected with the mystery pathogen, researchers across these public agencies discovered the potential severity of the disease course. In the early 1990s, a trio of published studies indicated that frequency of death from progressive liver disease was higher with the pathogen, with one positing, "surviving patients with chronic infection may yet die of liver disease" (Alter et al. 1992; DiBisceglie et al. 1991; Seeff et al. 1992). Taken together, these tracking studies elucidated more precisely the possible risks of the chronic but often asymptomatic course of the disease. This was no benign pathogen: the health of the public was at risk, especially as a generation of patients grew older. Yet scientists and

⁶⁶ The main METAVIR staging system is based on a Fo to F4 scale, in which Fo refers to the earliest stages of liver scarring, and F4 represents the latest stages when the liver is considered to be *cirrhotic* (Rosen 2011a).

clinicians remained vexed by the identity of the pathogen for much of this time; without its identity, and a diagnostic test for finding it in the blood, developing therapeutics remained out-of-reach prospects.

3.1.3 Identifying the pathogen: Chiron, the CDC, and the NIH

Unveiling this pathogen would require both the long-term efforts begun by the NIH on ‘non-A, non-B’ hepatitis as well as new breakthroughs in the field of molecular biology. A private pharmaceutical company Chiron used these breakthroughs, the long-term tracking work by the NIH, and collaboration with another government agency, the CDC, to crack the code behind the mystery pathogen.

In the years after the 1975 identification of a ‘non-A, non-B’ form of viral hepatitis, government scientists sought first to prove that the causative pathogen was indeed transmissible (Tabor et al. 1978b). At the NIH and Food and Drug Administration, scientists proved that the virus taken from patients in tracking studies could be transmitted to chimpanzee, resulting in similar liver abnormalities as in humans (enzyme elevations as well as histological changes) (Alter et al. 1978a; Tabor et al. 1978b). These experiments proved the infectious nature of the pathogen. NIH scientists also elucidated the pathogen’s structure through a series of studies to determine that it was likely a virus, given its small size, and had a lipid-based outer envelope structure (Feinstone et al. 1987).⁶⁷ Despite these crucial findings in the late 1970s and early 1980s, the pathogen remained elusive on a molecular level: absent its key identifying features, such as its genetic code, foreign structures that induced the body’s immune response (antigen), or the proteins making up the body’s defense against the invading agent, there was no way to detect the pathogen until it was already infecting liver cells. No one had pieced together the precise identity of the pathogen.

In 1983, a small biotechnology company, Chiron⁶⁸, became interested in this mysterious form of viral hepatitis as a potential business opportunity: by identifying the virus, the company believed they could develop diagnostic tests soon afterwards and generate millions in potential

⁶⁷ They used filtration and extraction-based methods to elucidate its size and viral nature. Filtration studies pass molecules through small, microscopic pores to identify potential size of pathogen, whereas extraction-based methods use a form of detergent to understand what kinds of chemical configurations compose the pathogen structure.

⁶⁸ Founded by three university scientists from Berkeley and University of California-San Francisco, the company represented an early wave of biotechnology companies using new molecular biology techniques and corporate partnerships (Fischer 1993).

sales to blood banks and transfusion services (Fischer 1993; Houghton 2009). Chiron's research program into identifying non-A, non-B hepatitis occurred over six years, until 1989, with the company reportedly investing approximately \$5-6 million each year which they had garnered from an initial public offering in 1983 and revenues from partnerships with larger companies (Fischer 1993).⁶⁹

A stark challenge lay before any scientist pursuing the pathogen: the blood of infected patients was not teeming with virus, making the search tantamount to finding the proverbial needle in the haystack (Alter and Houghton 2000; Houghton 2009). For the effort, they recruited a scientist fresh off his post-doctoral thesis that had involved new techniques from the rapidly evolving breakthroughs from molecular biology, Michael Houghton. After initially experiencing several rounds of failure in identifying the "needle in a haystack", Houghton's team turned to a) pivotal collaboration with the Centers for Disease Control and b) new tools in molecular biology developed through public funding (Houghton 2009).

In their early experiments, Chiron's scientists relied on old biological techniques, in which pathogens were identified via a *direct* discernment of 'viral structure'.⁷⁰ But with the virus not abundantly present in the blood stream, these approaches failed (Alter and Houghton 2000; Houghton 2009). Searching for blood more abundant with non-A, non-B pathogens, Houghton's team began working with Dan Bradley, a scientist at the Centers for Disease Control. In 1977, Bradley had started work on viral hepatitis when a company that produced blood clotting proteins for hemophiliacs became concerned that non-A, non-B hepatitis could be transmitted via its product (Bradley et al. 1979). After being approached by the company, Bradley began to test the hypothesis in chimpanzees. Upon confirming the company's suspicion, Bradley continued to develop the chimpanzee model and determined which chimpanzee samples had the highest levels of infection coursing through their blood plasma and liver.

Recent advances in molecular biology by 1985, however, allowed Bradley and another Chiron scientist, George Kuo, to propose an alternative, and ultimately fruitful route: cloning many, many copies of the virus, and then assessing its structure through *indirect* methods such as matching these copies with potential viral antibodies (Houghton 2009). By this strategy, called *blind immuno-screening*, cloned copies of genetic material from the infectious samples developed

⁶⁹ A decade later, Chiron would use this investment as a justification for its wide-ranging and contentious intellectual property claims on the Hepatitis C virus which I briefly highlight in the following chapter.

⁷⁰ For example, they tried to bind genetic material from infected livers with those of known viral genomes to see if there was any family semblance or relationship with existing viruses.

by the CDC's Bradley would be tested against antibodies from infectious patients. Rather than trying to find the needle directly, in other words, they came up with a 'magnet' – the antibody – and then attempted to find out whether the antibody would detect one of the cloned copies of the 'needle' (the virus) taken from Bradley's infectious chimpanzees (Houghton 2009). The approach worked: one of the cloned copies from the chimpanzees bound to the antibody. These molecular biology techniques were made possible through breakthroughs in manipulating genetic material made in the 1970s. These advances, pioneered by scientists Stanley Cohen and Herbert Boyer and funded by the National Institutes of Health, laid the technical basis for Chiron's strategy and an entire new sector of biotechnology (Cohen et al. 1973; Pisano 2006; Vallas et al. 2011).⁷³

One more major step remained in confirming the identify of the pathogen: testing whether this antibody would detect the virus not just in chimpanzees but in the infectious human patients that the NIH's Harvey Alter had tracked for over two decades. Multiple groups had approached Dr. Alter to see whether they had correctly identified the pathogen. Alter reflected, "By 1989, many different laboratories claimed to have developed a non-A, non-B assay and asked to test the panel. None were able to break the code and by 1989, the score was viruses, 20; investigators, zero" (Alter 2013:10). But at this point, Alter received a call from one of Chiron's scientist, asking Alter to trial Chiron's antibody test against the panel of blood he had carefully tracked over decades. To Alter's surprise, the Chiron test worked. He tested the pre-transfusion and post-transfusion samples, and found that the antibody tested *negative* in the pre-transfusion group, and *positive* in the post-transfusion group, just as would be expected from the right test. Fifteen years after identifying a non-A, non-B pathogen, scientists working across Chiron, CDC, and the NIH had solved the puzzle in 1989 (Choo et al. 1989).⁷⁴ They called the virus hepatitis C.

In sum, the post-war period to 1989 required an ascendant National Institutes of Health and a series of public sector organizations (including the Centers for Disease Control and Veterans Affairs) to pursue an unknown pathogen through patient investments. First, through

⁷³ Cohen and Boyer were able to use a kind of protein called 'restriction enzymes' to cut small, circular pieces of bacterial DNA called plasmids at specific, known sites, and then insert DNA from another organism into those gaps. The bacterial DNA then replicated in large numbers, proliferating the newly manipulated DNA and its proteins. This technical foundation was elucidated and developed through significant federal funding from the NIH, with the seminal studies by Boyer and Cohen along with Paul Berg conducted in the early 1970s. Their research paved the way for further experimental possibilities, with 123 NIH-funded projects funded by 1976 (Vallas et al. 2011).

⁷⁴ In a major award for the discovery of the virus, the Gairdner Prize - all three – Houghton from Chiron, Bradley from the CDC, and Alter from the NIH - were identified as key contributors (Wadman 2013).

long-term tracking studies of infectious patients, scientists at the NIH were able to identify the existence of a unique pathogen leading to a chronic but infectious form of hepatitis, which they dubbed non-A, non-B hepatitis. Second, by applying biochemical and histological analysis to these long-term tracking studies, publicly funded scientists across the NIH, CDC, and VA revealed that this form of hepatitis was not a benign entity, but rather the cause of a serious disease process that could end in mortality for a significant number of its human hosts. Finally, critical collaborations between Chiron and the CDC and NIH, along with new publicly funded advances in molecular biology, enabled the discovery and identification of the precise pathogen. Yet this early stage research would only mark the beginning of the scientific effort behind hepatitis C: further advances would rely on patient public capital to overcome a major technological hurdle posed by the virus.

3.2 Overcoming a technological hurdle: the replicon tool

Publicly funded scientists and agencies would go far beyond the ‘basic’ science for hepatitis C: they would develop the very technology required for drug development to begin. Far from conventional critiques of the state “crowding out the market”, risk-taking capital from the public sector helped “dynamize in” a market of private capital for investment in hepatitis C drug development. This technology – a research tool called the *replicon* – provided all potential drug developers – from large companies to small startup enterprises – with the necessary vehicle to test compounds against the virus. Rather than relying on indirect methods of attacking the virus, like the interferon-based therapies had done, the replicon also shaped the direction of the innovation process towards curative therapies, as drug developers could now pursue compounds which directly attacked the viral proteins on which the pathogen’s survival rested.

3.2.1 Growing a stubborn virus

This public risk-taking was pivotal because of a curious trait of the hepatitis C virus: the virus did not grow within cells, unlike most other viruses. Viruses are “*intercellular parasites*”, meaning they work inside of human cells and hijack its machinery to survive; typically, the efficacy of an anti-viral compound is evaluated by testing it within cells. Yet because the virus did not grow within cell cultures generated in laboratories, scientists could not test whether their compounds actually inhibited viral activity (Lindenbach and Rice 2005). The reasons for this stubbornness were unknown at the time, relegating scientists to studying the virus in bits and pieces. Drug development for hepatitis C could not progress, as scientists remained vexed by this

puzzle through much of the 1990s. Trials of different models yielded little success (Pollack 2003). One scientist lamented a “painfully slow process” and a “struggle to establish research tools and cell culture systems for HCV” as the rate-limiting factor for further advances in the field (Lindenbach and Rice 2005:689).

In the mid-1990s, German scientists began to pursue this puzzle, led by Ralf Bartenschlager at Heidelberg University and funded by the Germany Ministry for Research and Technology⁷⁶ and the German Research Society (Bartenschlager 2002). After initial attempts to reproduce the hepatitis C virus failed, they tried another route: instead of growing the entire Hepatitis C genome, what if they could reproduce just a part of it – the part that contained the main proteins involved in making more copies of itself? They were encouraged to pursue this idea based on the knowledge of other viruses with RNA code, which had shown that the outer proteins (called ‘structural proteins’) were not essential for replication (Bartenschlager 2002; Lohmann 1999b). Instead, they sought to construct a line of genetic code with only the internal proteins thought to be critical for Hepatitis C replication.⁷⁷ They then inserted this line of code (‘genome’) into *cancerous* liver cells (Huh-7 human hepatoma line) to see if copies of the virus could be produced (cancerous cells replicate at high levels, by definition). Upon analysis via various methods, Bartenschlager’s team ultimately found what they had long sought after: hepatitis C genetic material (RNA strands) of the anticipated size and correct subunits teeming inside the cancerous liver cells (Lohmann 1999b). In a reflection piece, Bartenschlager recounted the significance: “this first robust HCV cell culture model recapitulated all the intracellular step of the HCV replication cycle and because replication of these HCV RNAs relied on the viral enzymes, most notably the NS3 protease and the NS5B polymerase, the replicon system was suitable for drug development” (Bartenschlager 2002:913). In other words, drug companies could finally test whether their compounds worked against the parts of the virus – such as the NS3 protease and the NS5b polymerase – that enabled its replication. Inhibiting those parts could mean stopping

⁷⁶ Renamed the Federal Ministry for Education and Research as of 1998.

⁷⁷ Imagine a line of code made of different letters in alphabet (A-T-C-G), with groupings of these letters called ‘genes’ that produce particular proteins. Bartenschlager’s team replaced the genes that produced the outer proteins with a code used instead to produce an enzyme (NPT – neomycin phosphotransferase) that inactivates a cytotoxic drug (G418). Through this manipulation, they sought two consequences: first, the Hepatitis C RNA would no longer produce the outer proteins. Second, they could select only the cells that had produced enough of this newly manipulated RNA by applying the cytotoxic drug. This left Bartenschlager’s team with only the RNA that had the internal genes required for viral replication (Lohmann 1999b).

the virus, and the disease, in its tracks.

When veteran science journalist and writer Jon Cohen attended a NIH meeting on Hepatitis C in June of 1999, reports of the sub-genomic replicon were the “show stopper” (Cohen 1999b). The implications for drug discovery loomed large. Discussing Bartenschlager’s work, leading hepatologist Stanley Lemon shared, “if these results hold up, they’ll be enormously useful for drug screens” (Cohen 1999b:29). The group described the sub-genomic replicon in a November 1999 paper in *Science*, completing nearly five years of work (Lohmann 1999b).

Yet the replicon that Bartenschlager’s team had developed possessed significant limitations. Charlie Rice, a leading hepatitis C scientist in the US, noted: “Bartenschlager’s replicon was a landmark discovery in its own right, but the frequency with which you could initiate viral RNA replication was low” (Nair 2011). The Bartenschlager replicon was active in only 1 out of every 1,000,000 host cells, creating the need for an additional and cumbersome step of selecting the right cells in which to test potential compounds (Blight 2000). A scientist at Rockefeller University in New York, Rice had spent nearly a decade studying the virus with the support of the NIH and suspected that a further advance hung in the balance.

3.2.2 The NIH extramural program and the development of the replicon

With the identification of the virus in 1989, much of the focus on the part of the NIH had shifted towards a better understanding of the biology of the virus: this effort went far beyond the Bethesda-based campus, considered part of the NIH ‘intramural research program’, but instead to university laboratories across the US that receive grants through the NIH’s ‘extramural research program’. This de-centralized network of funding university scientists like Charlie Rice represents approximately 80% of the NIH’s budget and has become a core dimension of the US entrepreneurial state’s support of the innovation process in biomedicine.

The NIH doubled its overall budget in the 1990s, from \$8.9 billion in 1990 to \$15.6 billion in 1998 (and up to \$28 billion in 2004) (NIH 2017a). Though funding for hepatitis C trailed that of HIV research – with HIV garnering far more attention as a more acute infectious disease and immediate public health emergency – the growth in the budget directed towards liver research still out-paced the increasing overall NIH budget (Cohen 1999b). Much of this liver research was directed to viral hepatitis, with hepatitis C the leading disease of interest. Multiple NIH-led

forums and congressional testimony aimed to bring attention to hepatitis C.⁷⁸ Jay Hoofnagle (2004) the director of liver disease research at the NIH testified in 2004 to Congress:

“Let me point out that during this overall doubling of the NIH budget, funding for Hepatitis C increased nearly 5-fold, demonstrating the relative and emerging importance of research into this disease. Hepatitis C has been an area of high priority to the NIH during this critical period of our budget doubling”.

A primary method for funding these developments via NIH’s extramural research program was the R-01 granting mechanism given to senior scientists at universities across the US. These grants, which have been historically the longest and most widely used avenue for funding by the NIH, provide 3-5 years of funding disbursed annually over the period of the award (NIH 2016). Budgets for R-01 grants are *not capped*, giving applicants the flexibility to demonstrate the specific needs for the proposed amount (NIH 2016). These R-01 grants, combined with several other NIH funding mechanisms, would support Charlie Rice and his lab to build on the work of the Bartenschlager lab in order to make crucial improvements on the replicon tool (Blight 2000).

Rice’s team took the Bartenschlager replicon tool and aimed to make it reproduce at far higher rates (Blight 2000; Nair 2011b). Their strategy: hunt for genetic mutations that could enable the replicon to be more productive. Led by a scientist in Rice’s lab, Keril Blight, they rebuilt the replicon system using Bartenschlager’s data and the support from NIH grants that amounted to \$3.40 million between 1999 and 2003 (the years during which much of the replicon work was carried out).⁸⁰ This was part of an overall investment of \$10.8 million between 1993 to 2005 in Rice’s hepatitis C specific research.⁸¹

⁷⁸ The NIH held two “Consensus Development Conferences” (CDC)⁷⁸, one in 1997 and another in 2002, to synthesize the current state of knowledge on Hepatitis C from scientific, medical, public health vantages (NIH 2002). In testimony on March 5, 1998 to Congress, the former Surgeon General of the U.S., C Everitt Koop (1998), also signaled the looming consequences for failing to take action on Hepatitis C: “We have an infectious disease that is an undisputed threat to the public health. It is a viral disease that millions of people harbor without knowing they have it. [...] If we do not act, we will see a tragic increase in liver disease, in the demand for liver transplants, and in the death rate from hepatitis C related liver failure [...] I believe we have a 5-year window to identify and treat a significant proportion of the infected population if we are to head off the huge increase of liver disease I believe is ahead”.

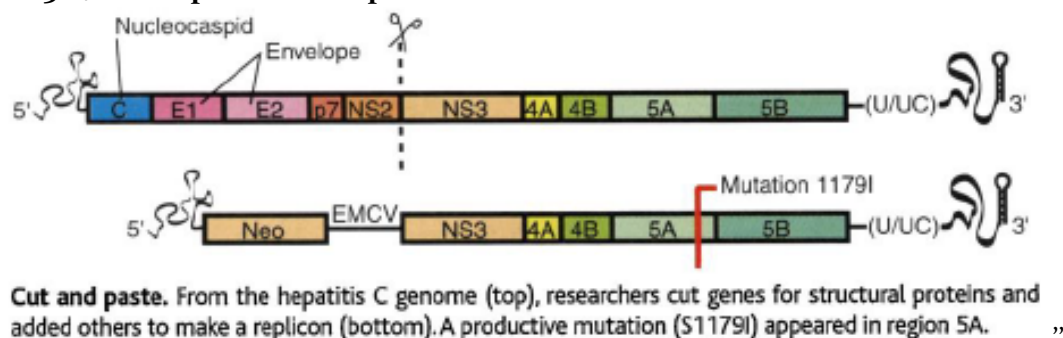
⁸⁰ NIH grants numbered CA57973 and AI40034 were listed as the two principal sources for their replicon papers in 2000 and 2002 (Blight 2000; Blight, McKeating, and Rice 2002). I examined each grant, which ran for both before and after the period of replicon research, between the years 1999 and 2003 to arrive at the \$3.40 million figure.

⁸¹ See Appendix B for further details on publicly funded grants and amounts.

They found the right mutations based on their use of a strain of the virus that was more infectious than the one used by the Bartenschlager team (Marshall 2000). Using these mutations, the Rice lab's replicon produced abundant viral proteins in one of out of 10 host cells, rather than one in 1 million, as was the case with the replicon developed by Bartenschlager's team in Germany (Blight 2000). "That really makes a big difference," Rice shared at the time, "It is going to allow us to do genetic studies on a much shorter time scale" (Marshall 2000). A fellow scientist, Francis Chisari, agreed with this assessment: "a major improvement in the efficiency of the replicon system that Bartenschlager developed" (Marshall 2000:1871). This replicon technology was further refined in the coming years by both the Bartenschlager and Rice labs, with drug developers eagerly awaiting the technology for use in their hunt for hepatitis C compounds.⁸⁴

To manufacture and distribute the replicon for wider use, Rice would need to search for further support. In order to rapidly share this new technology with the many companies that had previously shied away from hepatitis C drug development, Charlie Rice turned to a small biotechnology company named Apath that he had founded when he was still at the Washington University of St. Louis (Apath 2016).⁸⁵ Rice had envisioned Apath less as a profit-driven enterprise and more a vehicle for accelerating the fruits of his discoveries into the hands of other firms and scientists working on therapeutic advances (Marshall 2000). To make good on this vision for Apath and the replicon technology, Rice looked again to state investments.

Figure 3.1 / The replicon for hepatitis C



source: Science (2000), p. 1871

caption: This rendering shows the replicon on the bottom containing the critical subunits that enabled testing of compounds for hepatitis C.

⁸⁴ The replicon technology was expanded to include multiple subtypes (called 'genotypes') of the hepatitis C virus, such that drug developers could test compounds on all the variations of the virus which infect patients. See Horscroft (2005), Bartenschlager (2002), Blight (2003) papers.

⁸⁵ The existence and evolution of Apath was linked to the 1980 Bayh-Dole Act passed by US Congress, which enabled the private patenting of publicly funded research. I focus on this legislation and its consequences later in this chapter specifically in the context of Pharmasset.

3.2.3 Sharing the replicon widely with *the US small business program (SBIR)*

To meet its aim of sharing the replicon widely, Apath would look to a little-known government funding stream, the ‘Small Business Innovation Research’ (SBIR) program. Begun with a legislative act by the US Congress in 1982, the SBIR program requires government agencies with a research and development aim to ‘set aside’ a percentage of their budget for domestic small businesses that show a strong potential for technology commercialization (Ceulemans and Kolls 2013; Keller and Block 2013).

SBIR grew out of an emerging policy debate about the role of government in incentivizing innovation and private entrepreneurship during the 1970s and 1980s (Keller and Block 2013; Slaughter and Rhoades 1996). Senator Ted Kennedy, the iconic Democratic legislator from Massachusetts, wanted to make it easier for entrepreneurs to commercialize promising technologies and start new businesses (STTR 2016). To test whether the government could support this aim, Senator Kennedy led the passage of legislation to pilot a small business program within the National Science Foundation launched in 1977 (STTR 2016). With a successful launch within the National Science Foundation, the SBIR program was replicated across the federal government on a bipartisan basis through the passage of the 1982 SBIR Act (Keller and Block 2013). In order to further bridge a perceived gap between basic sciences and commercialization, Congress also passed the STTR (Science Technology and Transfer) program in 1992, in which small businesses must formally collaborate with a research institute (typically university and non-profits) to receive a grant (STTR 2016). The Small Business Administration has been charged with the responsibility of executing on these two programs across federal agencies.

SBIR and STTR work in a multiple-phase, decentralized manner (SBIR 2016). Federal agencies are given leeway to determine whether to use the funding as grants or contracts and to solicit proposals with narrow or broad specifications (Keller and Block 2013). The primary aim, however, is to fund pre-commercial technology development. All agencies with ‘extramural research budgets’ (such as the NIH or the Department of Energy) of over \$100 million are required to set aside a percentage of their research budgets for these programs (2.9% of their budgets as of a 2011 reauthorization bill). Each agency administers its own individual program within guidelines established by Congress, and designates areas for research and development in their proposal solicitations from small businesses (Keller and Block 2013). The intellectual property that

results from the research belongs to the firm, though the government retains the right to license the technology for an appropriate fee (SBIR 2016). In the decade between 2007-2016, National Institute of Health's SBIR and STTR programs together provided \$3.53 billion in grants to small business advancing products for biomedicine (National Institutes of Health SBIR/STTR program 2016). Across federal agencies, SBIR alone has self-reported the creation of 700 public companies due to its program from 1982 to 2016, with those companies attracting approximately \$41 billion in venture capital investments (SBIR 2016)

Two decades after its launch, SBIR would benefit Apath's efforts on hepatitis C. Apath received its first SBIR grant in 2001, a 2-year, \$750,000 package from the National Institutes of Health (Apath 2016). Though the first grant was aimed at hepatitis C diagnostics, the next grant, within less than a year, was a similar 2-year, \$750,000 grant from SBIR for further developing the replicon (Apath 2016).⁸⁹ During this time, Apath received a total of \$3.38 million from the NIH, with \$1.6 million from its SBIR program. In total from 1999 to 2008, Apath received over \$9 million in federal funding from the National Institutes of Health, with funding for research across anti-viral science. The funding specifically for the replicon gave Apath the capacity to build a business organization capable of manufacturing and distributing the replicon across academic and industrial laboratories. Labs awaited the replicon eagerly. One scientist, Stanley Lemon noted, that until now "it's been hard to get a system that was widely enough available so that people could play with it", continuing that "it will be great news if this innovation means that the technology will now be widely available" (Marshall 2000:1871).

In a *Science* article reporting on the discovery in 2000, Rice shared Apath's plans for commercializing the replicon (Blight 2000). In its early stages, Rice's team was determining whether they would make a few requests for company's use of the replicon, such as asking for a 30-day pre-publication review of scientific papers written by those who use the technology or negotiation with Apath on intellectual property rights should an inventor make a discovery using the technology (Marshall 2000:1871). But Rice made his strategic interests clear. Not wanting to do any thing that would "impede academic research", Rice went on to reassure the interviewer, "I think that sharing material for academic research should be done with as few strings as possible" (Marshall 2000:1871). Within two years, private and public labs began to acquire the replicon, as Apath offered non-exclusive licenses to use its so-called "Blazing Blight 7" technology, (referring

⁸⁹ See Appendix B for a listing of all SBIR grants made to Apath, derived from NIH Reporter database.

to its co-inventor Keril Blight, one of the scientists in Rice's lab). One of the many companies to buy Apath's replicon around this time would be a small start-up in Atlanta named Pharmasset that would go on to develop *sofosbuvir* (Pharmasset 2009).

In sum, publicly funded research proved pivotal at each stage of overcoming this technological hurdle that had previously prevented drug development. German agencies supported the Bartenschlager lab, and the NIH's extramural program supported Charlie Rice's modifications on the initial replicon technology. Additionally, the SBIR program enabled Rice's team via Apath to commercialize the technology and distribute it to companies at a small charge based on a non-exclusive license. The consequences for this support were significant: the replicon became used throughout the industry to test potential compounds that directly attacked the virus. Within the field of hepatitis C, it served as a kind of "general purpose technology" for hepatitis C, on which all future drug development was based.⁹¹ Dr. Marc Collett, then the head of discovery research for a small biotechnology company ViroPharma, noted its importance, "That's a definitely a breakthrough that every group has used" (Pollack 2003).

When the Lasker Prize committee in 2016 chose hepatitis C as the major medical advance on which to shine a spotlight, they awarded Rice and Bartenschlager *along with* Michael Sofia, the chemist who eventually developed *sofosbuvir* (Bartenschlager et al. 2016). Far from "crowding out" private funding, an entrepreneurial state *dynamised in* private capital, as companies began to see a potential clinical and economic opportunity in hepatitis C. Rather than tinker with indirect methods of attacking the virus, as the *interferon*-based regimens had done in boosting the body's immune system, the replicon enabled drug developers to find targets that directly halted the replication of the virus: this discovery thus also shaped the direction of the innovation process towards therapies that could result in increasing rates of cure.

3.3 The Triple Helix: Public and Private Science in the Launch of Pharmasset

In the spring of 1998, an Emory University scientist also based at Atlanta's Veterans Affairs hospital, Ray Schinazi, launched a company called Pharmasset. From the very beginning, his intentions were clear. "I coined that name," he would tell a reporter later, "it's actually

⁹¹ Examples of general-purpose technologies (GPTs) are the Internet, semi-conductors, nanotechnology; though the replicon is not a GPT on such a scale (and is actually based on other biotechnologies that *are* GPTs), the point is that the replicon had a widespread effect *within* the arena of hepatitis C drug development.

‘pharmaceutical assets’ and the idea was to create assets that would be sold to companies. That was the initial business plan” (Berkrot 2011). One of those assets would turn out to be *sofosbuvir*, the curative backbone for treating hepatitis C. Schinazi’s pursuit owed its genesis to multiple dimensions of an entrepreneurial U.S. state. The launch of Pharmasset resulted not only from long-term patient investments in science and risk-taking in commercializing that science, but also political-legal arrangements by the US government, exemplified by the Bayh-Dole Act, that enabled the conversion of publicly funded science into private assets.

3.3.1 The development of nucleoside chemistry and Pharmasset as public science

Schinazi benefited from decades of public support before starting his venture, with years of experience as a biochemist developing a new field of drug development: nucleoside chemistry. Under the tutelage of the ‘father of antiviral drugs’, William Prusoff⁹³, Schinazi had trained as a post-doc at Yale in the late 1970s after completing his doctoral research at the University of Bath in England (Cohen 2015). At Yale, he helped Prusoff’s team show that a ‘nucleoside analogue’, d4T, had activity against HIV (Cohen 2015). Nucleosides are chemical pre-cursors to nucleotides, which are the building blocks for DNA and RNA. Schinazi’s research focused on synthesizing ‘analogues’ to these nucleosides, which then get modified by the body and are taken up by viruses. When viruses incorporate these nucleoside analogues into their growing DNA or RNA chains (depending on the kind of the genetic material a given virus has), the analogues gum up the chain, block their further production, and abort the virus (De Clercq 2005). Schinazi’s research, beginning with Prusoff at Yale and then in Atlanta, focused on making nucleoside analogues into viable drugs. In the 1980s into the 2000s, large pharmaceutical companies shunned these compounds at the time, as they were deemed to be a high risk for causing harmful toxicities if they got into the production of genetic material in human cells (Cohen 2015). Two institutions would provide him with the long-term funding necessary to carry out the research for making safe and effective nucleosides: the Veterans Affairs administration⁹⁴ and the National Institutes of Health.

Schinazi came to Atlanta in the early 1980s, basing his laboratory at the Atlanta Veterans Affairs hospital while joining the faculty of Emory University (Cohen 2015). Since the early post-

⁹³ Prusoff had synthesized the first anti-viral ever used in clinical practice, a drug called idoxuridine that treats herpes infection of the eye (Cohen 2015).

⁹⁴ The Veterans Affairs hospital/health care system in the US is a publicly funded national system, akin to an ‘NHS for military veterans’.

war years, the VA had expanded a nascent set of research projects into a fully-fledged research program that had produced many notable contributions (Hays 2010).⁹⁶ Schinazi has credited the VA as an important dimension for his successes, as he enjoyed space for a staff of nearly 40 with what was considered to be the latest technologies as well as a state of the art animal research facility critical for pre-clinical testing of potential drugs at his 'Laboratory for Biochemical Pharmacology' (Emory University 2016). Additionally, Schinazi in nationally broadcast interview claimed that 7/8ths of his salary came from the Veterans Affairs systems during the 1990s and 2000s, with the remainder presumably from his faculty appointment at Emory (Reid 2015).⁹⁸ Schinazi would translate these resources for his research into new nucleoside therapies, most notably for HIV/AIDS and hepatitis C, both of which affect veterans in large numbers. For his work, he would later receive the William S. Middleton Award from the Veterans Affairs, the highest honor for biomedical research given by the agency (Veterans Affairs 2015).

Alongside the VA, the NIH served as Schinazi's other primary source of financial support. Like Charlie Rice, Schinazi was also the beneficiary of NIH's extramural funding program, with support from multiple programs, including R-01 grants as well as the special National Merit Award (NIH 2017b). The National Merit Award goes beyond the R-01 program by recognizing scientists deemed to be exceptional with the opportunity to pursue projects with 'greater risks' that are 'more adventurous' that take time to develop: these awards are given typically for *no less* than 5 years, and can be renewed for a total 10-year window of research (NIH 2017b).⁹⁹ Starting in the early 1990s into 2011, Schinazi translated \$8.4 million in different NIH funding streams towards his nucleoside research.¹⁰⁰ By the late 1990s, Schinazi had developed multiple compounds

⁹⁶ In 1955, Congress first appropriated a research and development budget for the VA system. The VA system has produced breakthroughs such as the first cardiac pacemaker (1958), concepts that led to the development of the CAT scan (1960), and liver transplantation (1968) (Hays 2010). In 2016, the VA research budget was \$1.8 billion.

⁹⁸ A US Congressional hearing in 2016 related to *sofosbuvir*'s cost to the VA health care system focused on the VA's limited disclosure policies related to products and patents generated using VA funding (Flier 2016). The VA relies on 'self-report' from scientists themselves, diminishing the agencies ability to gain royalties from potential licenses. In FY 2014, the VA earned only \$375,674 in royalties (Flier 2016). By contrast, the NIH's intramural program, which has more than double the budget of the entire VA's R&D program, earned \$137 million in royalties (Flier 2016).

⁹⁹ According to a separate analysis performed by the access to medicines group Knowledge Ecology International, Schinazi was a principal investigator of 64 NIH grants between 1991 to 2012, involving \$10.5 million in public funding. He filed a total of 49 patents that disclosed federal funding, with the NIH and VA listed as two of the principal federal agencies. This figure is larger than my \$8.4 million finding, because it includes non-nucleoside science related research (Love 2014a).

¹⁰⁰ See Appendix B with data for grants listed, based on NIH Reporter database.

that could serve as leading candidates for development. One compound, *emtricitabine*, showed particular promise for HIV (Cohen 2015). Schinazi launched a company called Triangle Pharmaceuticals in 1996 to further develop the compound in clinical trials (Cohen 2015). In 2004, the compound would get acquired for \$464 million by a familiar company: Gilead Sciences (Cohen 2015).

With Triangle focused on developing *emtricitabine*, Schinazi launched Pharmasset as a vehicle through which a larger array nucleoside compounds could be developed into valuable ‘assets’ for larger pharmaceutical companies that were still shying away from early-stage nucleoside science from the fear of toxicities. He positioned the company as a nodal point in a network of publicly funded research universities in the Atlanta area, drawing on the libraries of compounds that were being produced in these university laboratories. An Atlanta Business Chronicle article described the configuration: “Schinazi has a team of 30 researchers at Emory continuing to discover new drugs. Liotta has about 15 researchers and another founder, Chung Chu at the University of Georgia, has about 20. The fourth founder is scientist Jean Pierre Sommadossi of the University of Alabama at Birmingham” (Robbins 1999). Schinazi went on to extol the comparative advantage of the early-stage employees at his new company: “Most of them are top scientists from around the world who bring more than 100 patents and the beginnings of 8 potential drug formulas to the company” (Robbins 1999). This configuration – of taxpayer funded research happening at universities and used to support a small biotechnology company like Pharmasset – was enabled through a political-legal shift that had occurred nearly two decades earlier.

3.3.2 The Bayh-Dole Act and the Conversion of Public Assets

The early 1980s witnessed a marked shift in the political-legal rules governing science and technology in the US. The dominant narrative behind this shift: policy makers on a bipartisan basis saw the need to respond to the economic malaise of the 1970s, and one route they foresaw was to promote business through the commercialization of new advances in science and technology (Mowery and Sampat 2004; Rai and Eisenberg 2003). This vision was to be realized, in part, through direct funding of small business and regulatory changes encouraging private actors to commercialize knowledge developed in federal laboratories and with public funding (Boettiger and Bennett 2006). The purported goal from such a shift was two-fold: promote jobs through high-tech industries and gain an edge in an increasingly competitive global market (Slaughter and Rhoades 1996; Vallas et al. 2011). A raft of changes unfolded in the 1980s (see table below), making

it easier for a nascent biotechnology sector and pharmaceutical sector, for example, to take advantage of new knowledge generated via public funds.

One specific change came with the 1980 passage of the Bayh-Dole Act, which permitted inventions developed with public funds to be patented by a university or a professor rather than be assigned to the government (Rai and Eisenberg 2003). Before the Bayh-Dole Act, such a move would not have been possible due to public ownership rights over research. Reflecting on the moment, an administrator at Ray Schinazi's Emory university reflected, "The theory was that a lot of innovation was coming out of federally funded research, but it was all owned by the government and 'sitting on the shelf'" (Robertson 2015). That administrator, Todd Sherer, was the head of Emory University's Technology Transfer Office (TTO), a new kind of office launched across American universities in the 1980s and 1990s (Robertson 2015). TTOs worked with university professors to apply for patent protection over their discoveries and support the commercialization process (Mowery and Sampat 2004). This new legal set-up shifted the stakes of research: for university administrators, all research generated by faculty could now be valuable intellectual property, and for university professors like Ray Schinazi, all discoveries could now be converted to private, licensable products attracting capital rather than serving as knowledge in the public domain (Mowery et al. 2001).

Schinazi and Emory took advantage of this change in the mid-1990s, when his laboratory iterated on a prior discovery by a Canadian scientist to develop *emtricitabine* for HIV/AIDS patients in 1996 (Cohen 2015). Emory patented the compound, which Schinazi had developed with public funding, and then licensed it later to Triangle Pharmaceuticals, Schinazi's spin-off business (Cohen 2015). When Gilead later bought Triangle for its *emtricitabine* compound for \$464 million and then began selling it as part of a combination therapy in 2004, Emory University gained \$540 million in royalty payments – the largest royalty payment to a university at the time (Emory University 2005).¹⁰¹

The Bayh-Dole Act and the broader regulatory shifts of the 1980s are a contested terrain that I do not explore at greater depth here.¹⁰² What is clear, however, is that this period signified a

¹⁰¹ In an interview with university media after the deal, Emory's university president affirmed the 1980 law, saying, "The elements of our strategic plan that are research related and consistent with the Bayh-Dole Act provisions will benefit from these moneys." (Emory University 2005).

¹⁰² The Bayh-Dole has sparked multiple interpretations, with advocates pointing to it as a positive force behind innovation in the US and others describing its deleterious effect in privatizing science (Boettiger and Bennett 2006; Kenney and Patton 2009; Mowery et al. 2001). I do not engage in these broader debates

break from previous pathways for innovation. The STS scholar Sheilla Jasanoff articulated, for example, that Bayh-Dole “changed the long-standing presumption that publicly funded work could not be privately owned and exploited” (Jasanoff 2011:235). Gary Pisano, in his work on the emergence of the biotechnology sector, detailed the shift in incentives for publicly-funded scientists: knowledge assets were now to be monetized, incentivizing academics to pursue a direct economic interest via shares in a new company as well as attempt to attract external investors to sustain and expand research efforts (Pisano 2006). This configuration of university labs, public funding, and small enterprises has been dubbed a “triple helix”, with many innovations tracing their genesis to this triad

In this sense, the Bayh-Dole Act promulgated a new political-legal contract to convert public science into private assets, and spawned an organizational apparatus to support the commercialization process. Such a contract contained a risk: the government could forfeit its right to knowledge that would later be of public concern. Rooted within the Bayh-Dole Act was a “march in” provision, which enabled the US government to license any intellectual property that emerged from federally funded research in the case of public health need (Kesselheim 2011; Rai and Eisenberg 2003). As of 2016, the provision had never been exercised. In the meantime, university professors like Ray Schinazi would operate within this political-legal contract and organizational apparatus as he pursued his hepatitis C research.

Table 3.3 Regulatory shifts favorable to biotechnology commercialization in 1980s

Year	Legislation/rule change	Significance
1980	Bayh-Dole Act	Permitted inventions developed with federal funds to be privately patented and owned rather than assigned to the government
1980	Stevenson-Wydler Technology Innovation Act	Promoted federal laboratories to transfer technology to non-federal entities; required federal laboratories to set apart a percentage of budget towards tech transfer activities
1982	Small Business Innovation Act	Created system of grants for small business, promoted direct federal financial support of commercialization
1980	Diamond vs. Chakrabarty Supreme Court ruling	Made it legal to patent genetically modified organisms; enabled upstream patenting
1986	Federal Technology Transfer Act	Expanded Stevenson-Wydler (1980) to create ‘CRADA’ framework – cooperative research and development agreements – between federal government and commercial sector for technology transfer

Sources: Slaughter (1996) and Vallas (2011)

here but point to its influence in enabling Pharmasset to commercialize publicly funded nucleoside research.

3.3.3 Public risk-taking on Pharmasset

By the late 1990s, starting a company from publicly funded research at a university had become a more common practice. As I described earlier, Schinazi had already done it once, with Triangle Pharmaceuticals (Cohen 2015). With the idea to start a new company to take on a wider range of nucleoside compounds for viral diseases, and the legal space within which to do it, Schinazi looked to attract financing. One source would be venture capital, a kind of finance I describe in the next chapter. Yet another key source remained the US state. Not only did funding from public agencies such as the NIH and VA provide a base of knowledge on which to found Pharmasset, but the NIH's SBIR program also took risks on those assets to develop them further.

Between the initial founding in 1999 to the discovery and development of the more efficient replicon by Apath in 2002, Pharmasset's focus remained on other nucleosides for HIV and HBV (Robbins-Roth 1999). After the development of the replicon, however, the NIH granted Pharmasset funding for hepatitis C, as drug discovery only then began in earnest across the industry. Over the course of the company's first seven years, the NIH would support Pharmasset with \$2.46 million in public financing through 16 SBIR grants, like the ones given to Apath LLC for the sub-genomic replicons. Of these, six grants between 2002-2004 supported Hepatitis C drug development specifically, at a cost of \$1.01 million.¹⁰³ This money also came in parallel with over \$50 million in private venture capital, which I analyze further in the next chapter when I focus on private financial capital.

Though the venture capital funding outsized Pharmasset's initial NIH funding, these SBIR grants still proved critical to Pharmasset's early formation. As Block and Keller describe, the importance of SBIR grants are not limited to the amount of money itself. SBIR grants provide a kind of "signaling and certification" mechanism to venture capital (Keller and Block 2013:644).¹⁰⁴ Keller and Block traced the relationship between venture capital and SBIR grant in five different years between 1995-2009 (Keller and Block 2013). In the life sciences in particular, they found that between 1995 and 2009 roughly 20% of venture capital investments were made to firms that had

¹⁰³ As one of its promising compounds later moved through initial clinical trials, Pharmasset would also be a beneficiary of the Affordable Care Act when a little-discussed provision created a \$1 billion fund for applications for projects 'that showed significant potential to produce new and cost-saving therapies, support jobs and increase U.S. competitiveness'. The modest federal grant of \$244,479.25 specifically supported the 'development of PSI-7977' under the Qualifying Therapeutic Discovery Program.

¹⁰⁴ Keller and Block (2013) write, "The relationship between SBIR and VC is permeated by multiple logics in which venture capitalists use SBIR as a signaling and certification mechanism—investing in ideas developed through the program—and that they also use the program to develop ideas they already find promising."

previously received one or more SBIR awards (Keller and Block 2013).¹⁰⁵ Pharmasset was one of these firms, as venture capital came alongside these SBIR grants; the company featured each of its 14 SBIR grants prominently on their website, showcasing them to potential investors on their website as badges of public support.

Table 3.4 Timing of NIH SBIR grants and venture capital rounds

Year	NIH funding	# of grants	Venture capital round?
1999	0		X (Series B)
2000	\$442,011	4	
2001	\$630,461	4	X (Series C)
2002	\$553,207	3	
2003	\$450,260	3	
2004	\$189,277	1	X (Series D)
2005	\$194,954	1	
TOTAL	2,460,170*	16	

Figure 3.2 Screenshot of Pharmasset website, May 2002

STTR-EBV	January 7, 2002 - Pharmasset, Inc. Receives NIH-STTR Grant for Nucleoside Chemistry Research on Epstein-Barr Virus (EBV)
SBIR-HBV	November 29, 2001 - Pharmasset, Inc. Receives NIH-SBIR Grant for Antivirals Against Hepatitis B Virus (HBV)
SBIR-Azide	August 24, 2001 - Pharmasset, Inc. Receives NIH-SBIR Grant for Antiviral and Anticancer Drug Delivery Technology Based on Azide Nucleosides
SBIR-Benzamides	May 29, 2001 - Pharmasset, Inc. Receives NIH-SBIR Grant for Novel Colon Cancer Drug Development
PSL-TVM	March 14, 2001 - Pharmasset, Ltd. Received Major Private Placement by TVM Techno Venture Management
New_Directors	November 6, 2000 - Pharmasset, Ltd. Shareholders Approve Two New Directors
SBIR-Racivir	October 10, 2000 - Pharmasset, Inc. Receives NIH-SBIR Grant for <i>Racivir</i>TM for Treatment of Hepatitis B and HIV Infections
DCP-2nd	October 10, 2000 - Pharmasset, Ltd. Announces Additional Equity Investment by DuPont Pharmaceuticals Company
	August 15, 2000 - Pharmasset, Inc. Receives NIH-SBIR Grant for the Development of Novel Cofactor Analogues as Immunosuppressants
	May 8, 2000 - Pharmasset, Ltd. Announces Additional Equity Investment By MPM
	May 8, 2000 - Pharmasset, Inc. Receives NIH-SBIR Grant for the Development of L-Nucleosides as Anti-HBV Agents
	March 6, 2000 - Pharmasset, Inc. Receives NIH-SBIR Grant for Human Leukemia Research

Source: Wayback Machine

Caption: Pharmasset displayed their NIH grants on their website, a badge of approval and signaling mechanism used to attract other investors. Eight SBIR or STTR grants are showcased between 2000 and early 2002. Pharmasset's first Hepatitis C related SBIR-STTR grant came later in 2002, which was not available for retrieval from the Wayback Machine.

¹⁰⁵ Keller and Block argue that this is a striking figure, given that SBIR only represents 2.5% of all federal extramural research and development funding and is rarely cited as an important source of funding for biotechnology development (Keller and Block 2013).

3.4 Following an entrepreneurial state: a summary

This chapter shows how patient investment, confrontation with uncertainty and risk, and deal-making by an entrepreneurial state set private capital in motion for hepatitis C drug development and shaped the direction of the innovation process towards a curative therapy. In short, a shadow epidemic became visible, which in turn mobilized the search and development of its antidote.

First, through the emergence of the NIH in the post-war era, scientists engaged in long-term tracking of the disease process before the virus was even identified. Without this long-term tracking, scientists, public health officials, and drug companies could not have known the seriousness of the health consequences posed by the hepatitis C virus. This tracking also provided the samples pivotal to confirming the discovery of the virus.

Second, through the NIH's upstream-downstream funding mechanisms – via its extramural research program as well as the Small Business Innovation Research program – an entrepreneurial state overcame significant technological obstacles to shape the creation and direction of a new market for drug development in hepatitis C. The discovery and the development of the replicon – facilitated by the German state as well as the US NIH – enabled drug companies to begin trialing potential compounds that directly attacked hepatitis C, thereby shaping a path towards a curative therapy. The NIH specifically enabled the Rice lab to not only develop a more efficient replicon but also to manufacture and distribute the research tool widely in the early 2000s.

Third, the US entrepreneurial state both funded the long-term nucleoside science behind Pharmasset and made investments in its earliest stages and also created the legal contract in the Bayh-Dole Act via which the company could convert its public assets into private ones. An entrepreneurial state behind hepatitis C thus took on crucial roles in the innovation process: patient investing in the upstream-downstream science necessary for elucidating the virus and developing therapies, risk-taking in breakthrough technologies to overcome technical obstacles to curative drug development, and governing the conversion of public assets for the creation of new organizational entities such as Pharmasset.

Each of these three threads converged to set the direction of the innovation process towards a curative therapy and attract private capital to take advantage of the emerging economic opportunity. *Yet the Bayh-Dole Act also created the conditions for a particular mobilization of this private capital, in which Pharmasset would look to speculative capitals (ranging from venture*

capital to an eventual initial public offering) for the development of its intangible pharmaceutical assets. As I describe in the subsequent two chapters, this configuration would be one of the critical inputs towards the financialization of hepatitis C drug development and *sofosbuvir's* pricing.

Large pharmaceutical businesses did not appear in these early stages of the innovation process. Until the development of the replicon, these firms largely stayed on the sidelines of the innovation process. Small biotechnology companies and venture capital also were mobilized once the replicon had been developed. Furthermore, the small biotechnology company critical to the *sofosbuvir* innovation process, Pharmasset, can be traced back to long-term public support from the Veterans Affairs administration as well as the NIH's extramural research program funding via Emory University. By this initial accounting, taxpayers via public sector organizations took on pivotal risks in the innovation process behind hepatitis C. While this chapter captures the role of public sector organizations, the entrepreneurial state makes crucial reappearances later in the drug development process that will enable a more detailed accounting of its role in the innovation process. Whether the rewards to the public sector are proportionate to this risk-taking requires onwards analysis into the downstream stages of the innovation process. We turn to these stages in chapter four.

Chapter 4. Chasing the Golden Snitch: Speculative Capital and Shareholders behind *Sofosbuvir*

“Harry was speeding toward the ground when the crowd saw him clap his hand to his mouth as though he was going to be sick – he hit the field on all fours - coughed - and something gold fell into his hand.

‘I’ve got the snitch!’ he shouted, waving it above his head, and the game ended in complete confusion.

...Harry hadn’t broken any rules and Lee Jordan was still happily shouting the results - Gryffindor had won by 170 points to 60.”

- JK Rowling, in *Harry Potter and the Sorcerer’s Stone*, describing Harry’s chase for the golden snitch

With the advent of the replicon in the early 2000s, the race for new medicines to tame the hepatitis C virus expanded, as drug developers were finally able to test compounds that directly attacked the virus. Two businesses formed the foreground of this race: Pharmasset, controlling the development of *sofosbuvir*, and Gilead Sciences, a large business in pursuit of new growth beyond its sales of HIV medicines. As Gilead’s senior leadership evaluated its prospects in hepatitis C in the summer of 2011, they turned to the world of fiction to give their high stakes game plan a name: Project Harry (United States Senate, Committee on Finance 2015). In the famed fantasy series by JK Rowling, Harry Potter and his competitors play *quidditch*, a game in which there is one goal: to catch the *Golden Snitch*. Though multiple types of balls zoom around in the field of play, only one – the Golden Snitch – guarantees an automatic victory. The analogy to drug development for hepatitis C fit. Finding the best therapy to hepatitis C would mean winning in one of the largest potential pharmaceutical ‘markets’ available. This chapter chronicles this game, focusing on the development of *sofosbuvir* across the multiple state, business, and financial actors that constituted the pre-clinical research to late stage trials for compounds aimed to treat hepatitis C.

Through chronicling this game, I introduce the influence of *financialization* on the eventual launch prices for *sofosbuvir*. With the financialization of drug development, a chain of financial actors engaged in a pattern of accumulation aimed at growth through the capitalization and control of intangible assets in financial markets. In this chain, for example, Pharmasset mobilized over \$50 million in venture capital, launched an IPO of \$45 million, and would later be

acquired for \$11 billion – even though the company never developed an approved medicine or produced profits. This chain of speculative capital rested on the opportunity to make gains on short-term bets in financial markets of intangible hepatitis C assets. The valuations of these intangible assets, in turn, was held up by the promise that health systems would pay for rising prices in exchange for improved therapeutic outcomes for larger patient populations (what I refer to as the *pricing escalator*).

For Gilead, a large publicly traded business, extractive logics driving its shareholders meant that profitability alone would not do – shareholders valued the company based on its (1) potential to generate near-term growth at a magnitude greater than competing vehicles for capital accumulation (what I call the *shareholder growth treadmill*) as well as its (2) distribution to shareholders of earnings that executives deemed could not be used to generate such growth. With long-term investments in drug development at odds with these shareholder demands, Gilead used its accumulated capital to gain control over Pharmasset for *sofosbuvir*'s anticipated earnings stream – and then distributed the bulk of its eventual hepatitis C revenues to shareholders (rather than long-term reinvestments in research). Through this combination of speculative capitals and extraction driven by Gilead's shareholders, the prices and valuation of *sofosbuvir* along the innovation process became fastened to the logics, institutions and relations of power at play in financial markets – not the tangible costs of innovation or embodied health improvements experienced by patients.

The state, rather than receding into the backdrop, continued to play a pivotal role in the innovation process, as the application of public science from a decade earlier ultimately transformed one of Pharmasset's hepatitis C assets into *sofosbuvir*. The US state also governed the rules of control for capital – with the emergence of venture capital and the rise of shareholder control over businesses both due in part to shifts in regulation.

In this chapter, I detail these dynamics underpinning the financialization of *sofosbuvir* in four parts:

First, I follow the mobilization of speculative capitals behind Pharmasset (section 4.1). In this case, Pharmasset developed a promising new compound called *sofosbuvir* with venture capital, licensing partnerships with larger businesses, and the stock market, with each set of financial actors making bets on the anticipation of rising prices and valuations for hepatitis C assets. I describe how the state's governance over the rules of capital enabled the formation of speculative financial markets, and also how the key scientific advance that shaped *sofosbuvir*'s

curative potential came from state-supported knowledge. To compose this account, I weave together Pharmasset's filings with the Securities and Exchange Commission, scientific and medical journals detailing chemical and clinical advances, and interviews with scientists.

The second part (section 4.2) traces the structural crisis created by shareholder control over Gilead Sciences. I show how shareholders valued Gilead and other established¹⁰⁸ pharmaceutical businesses not on their sales and rate of profitability but by their potential to grow. Combining media accounts and Gilead's financial statements with existing histories of the rise of shareholders and the company's early trajectory, I follow Gilead from its genesis to trace the influence of this shareholder control on Gilead's position in the innovation process less as a research and development company and more as an acquisition specialist.

In part three (4.3), I document Gilead's use of their accumulated capital to attempt to transcend their shareholder-driven crisis of growth by acquiring Pharmasset for \$11 billion and gaining control over the stream of earnings anticipated from *sofosbuvir*. I unpack Gilead's valuation of Pharmasset - through its capitalization exercise - as a strategic site of analysis in the innovation process that reveals the broader relations of power between Gilead and three actors: with small biotechnology companies like Pharmasset, the public health delivery state, and shareholders. A close analysis of the acquisition comes from interviews with industry executives as well as internal documents from both Pharmasset and Gilead in the US Senate investigation. Through media accounts, I also show how Gilead's acquisition of Pharmasset triggered a series of acquisitions for hepatitis C assets, illustrating the ways a struggle for growth between competing businesses escalated the speculative costs of innovation in the late-stages of drug development.

In the final part (4.4), I follow Gilead's financial statements to show the destination of their hepatitis C earnings. Rather than reinvesting their hepatitis C revenue into research and development or pay taxes, I demonstrate that regulatory shifts by the US state enabled Gilead's senior executives to channel much of these earnings into share repurchases designed to boost the value of its remaining shares to shareholders - with a significant shareholder being Gilead's executives themselves with the rise in stock-based compensation. After describing each of these parts, I conclude by (in section 4.5) taking stock of the key political-economic dynamics in this phase of the innovation process.

¹⁰⁸ By 'established', I am referring to the large, incumbent businesses that have experienced long-term profitability and are publicly traded, in contrast to small biotechnology companies that often have no approved products or sales.

4.1 Sofosbuvir's development and financial markets of pharmaceutical assets

The early 2000s brought an expanding search for hepatitis C therapies, with the replicon drawing in an expanding field of emerging companies and speculative capital.¹⁰⁹ This section follows the process by which speculative capitals¹¹⁰, varying in its multiple forms from venture capital to public equity in stock markets, mobilized behind Pharmasset and *sofosbuvir* (see Table 4.1 for a summary of each of the primary sources for Pharmasset's capital). The lure for these different capitals was not Pharmasset's anticipated profitability and sales from approved products – the company had a \$313.9 million *deficit* over the course of its existence – but rather on the promise of growing valuations for hepatitis C assets (Pharmasset 2009). This growing valuation was in turn underpinned by the phenomenon of a *pricing escalator*, in which future prices were expected to be higher than those of the existing standard of care. The owners of this capital did not aim to finance Pharmasset's drug development to the point of approval and sales – but rather aimed to make bets in increasingly liquid financial markets (from venture capital to NASDAQ) for rewards within time horizons far shorter than the time (ten years) it took to develop *sofosbuvir*.

Along the trajectory of these stages in the innovation process behind *sofosbuvir*, the imprint of public organizations and state policy remained, as the application of public science transformed the curative potential of one of Pharmasset's early hepatitis C assets (PSI-6130) and ultimately manifested in the *sofosbuvir* compound. Furthermore, technological and regulatory shifts undertaken by the US State in the 1970s into the 1980s led to the formation of these financial markets of speculative capital for pharmaceutical development. This speculative process in the early stages of drug development, which involved multiple financial actors, business organizations, and the state, was a central element in the financialization of drug pricing and

¹⁰⁹ Along with the replicon development, another development also supported investment in hepatitis C research: Chiron loosened its previously prohibitive intellectual patent protections over hepatitis C after pressure from the US Centers for Disease Control in 2004 (P. Elias 2004). During the 1990s and early 2000s, Chiron had set up barriers to research in the area by charging significant licensing fee and royalties based on their patents after the identification of the pathogen in 1989 (Cohen 1999a).

¹¹⁰ My usage of the term 'speculative capitals' is marked by two features. First, I use the term 'speculative' to refer to the short-term and exit-oriented nature towards these forms of capital. This contrasts with more 'patient capital', as defined by Deeg and Hardie (2016) by their intention towards long-term investment, performance measured through creditworthiness (and I would also add 'learning') rather than share price, and likelihood of maintaining investment (rather than exit) in face of adverse firm conditions. I also use 'capitals' in plural to refer to the different types of such speculative capital - ranging from venture capital to equity traders on the stock market – which vary in extent of patience and expectation of return.

innovation. I drew on Pharmasset's financial filings, articles in medicinal chemistry journals, the US Senate Finance Committee report as well as interviews to follow this process.¹¹¹

Table 4.1 Pharmasset's sources of financing, 1999-2011 (all figures in millions)

Period	Financing source	Amount
2000-2005	SBIR	\$2.46
1999-2004	Venture Capital	\$53.81
2004-2010	Roche partnership	\$44.50
2007	Initial public offering	\$45.00
2008-2011	Follow-on equity financing	\$345.87
	TOTAL FINANCING, 2011-2011	\$491.66
	TOTAL OPERATING LOSS, 2001-2011	-\$313.9

Sources: Pharmasset SEC filings, S&P Capital database

4.1.1 Pharmasset's early assets and the entry of venture capital

As Pharmasset embarked on developing its early pharmaceutical assets in the early 2000s, they searched for potential sources of financing to carry forward their research efforts. *Venture capital* would enter this stage of the innovation process, aiming to generate a return through investments in Pharmasset's intangible pharmaceutical assets. Section 4.1 first situates these venture capital investments in Pharmasset in the context of other financing sources, then describes the mechanisms of pricing and valuation used by venture capitalists to pursue their strategic interests in the innovation process, and ends by linking regulatory shifts by the US state to the genesis of venture-backed biotechnology businesses like Pharmasset.

Neither direct public funding beyond NIH's SBIR program nor bank financing would comprise Pharmasset's search for capital. Though the state had been a critical source of patient capital for Schinazi's efforts to arrive at this stage, the SBIR grants highlighted in the previous chapter would not be sufficient for entering compounds into the phase I and II trials that typically run into the millions: an average anti-infective clinical trial in a single Phase I can be \$4.2 million, with a Phase II trial amounting to \$14.2 million, according to a US government study using 2004-2012 data (Sertkaya et al. 2016).¹¹² While hepatitis C was a growing public health concern in the

¹¹¹ Interviews 12, 13, 15, 26, 27, 28, and 35 contributed to understanding Pharmasset's early stage financing and ultimately the development of *sofosbuvir*.

¹¹² See Sertkaya (2016) for more on clinical trial data

late 1990s and 2000s, the NIH had not developed a strategic ‘mission-oriented plan’ to scale-up financing of hepatitis C drug development, particularly public funding of clinical trials (Cohen 1999b).¹¹³ This lack of mobilization contrasts with the case of HIV/AIDS, in which political movements had instigated a broad-based public-sector driven approach to drug development (see Broder 2010).¹¹⁴ Similar political support had yet to be engendered for hepatitis C in national capitols, with the chronic and often invisible nature of hepatitis C combined with the marginalized status of many patients with the virus as potential reasons for this relative silence (Groopman 1998). Banks, in the meantime, would also not be a viable option for Pharmasset. The high levels of uncertainty and the lack of collateral from approved products for small biotechnology companies like Pharmasset make them unsuited for bank financing (Hopkins et al. 2013; Robbins-Roth 2001).

Instead, by 2004, Pharmasset had raised \$55.3 million in venture capital to finance their nucleoside development work (S&P Capital IQ 2016b). This financing came in staged equity rounds, from a seed stage to series B, C, and D.¹¹⁵ Each round escalated the capital investment amount in parallel with the valuations of the company made by the given venture capitalists in that round: from \$3.91 million in its Series B round in June 1999 to its Series D round of \$40 million in August 2004 (S&P Capital IQ 2016b).¹¹⁶ A different venture capital fund led each round, with two focused mostly on drug development (MPM Capital and Burrill and Company) and a third (TVM) investing across information technology as well as life sciences domains (S&P Capital IQ 2016b). These venture funds, like others similar funds but in contrast to the US state, provided financing to Pharmasset in return for an ownership stake in the company (Robbins-Roth 2001).¹¹⁷

¹¹³ While major public investments shaped the direction of the innovation process for hepatitis C towards a cure, the absence of a larger ‘mission-oriented’ strategy inclusive of public funding of clinical trials in this case was a critical limitation of the entrepreneurial state in the case of hepatitis C.

¹¹⁴ Broder (2010) tells story of NIH’s collaboration with Burroughs-Wellcome, now Glaxo-Smithkline (GSK) to develop first anti-retrovirals.

¹¹⁵ For Pharmasset, this seed round was not publicly reported; from personal communication with the founders of the company, as well as individual public statements on deals with allied companies, I calculated that Pharmasset raised approximately \$2.5 million in this initial round. Two million came from selling licensing of compounds with two companies, one in Boston and another in Brazil, with the remaining funds coming from a range of smaller contributions from \$10 to \$500K.

¹¹⁶ These rounds mirrored the typical ranges for small biotechnology ventures in the late 1990s and early 2000s.

¹¹⁷ Neither the VA nor the NIH, both of which had supported Pharmasset, had any ownership stake in Pharmasset as it developed.

Yet when Pharmasset raised \$40 million in a series D round of venture financing in 2004, the company had no approved products, had run an operating loss in each year since its founding (for a total of \$15.8 million in deficits), and was not expected to generate profitability for years into the future (Pharmasset 2006). *Why did Pharmasset then attract this venture capital?* Three dynamics reveal the interests of venture capitalists as well as the pricing and valuation practices that underpin their position within the innovation process.

The first dynamic is that venture capitalists aim to gain financial rewards not on the profitability of a newly approved or existing drugs, but via mobilizing publicly-funded science into downstream financial markets in which they can exit their ownership of an investee firm (Lazonick and Tulum 2011.; Pisano 2006; Robbins-Roth 2001). Venture capitalists typically maintain their ownership stakes for three to five years, and are focused on exiting through either an acquisition of their investee firm by a larger business, or via an initial public offering, in which venture capitalists can transfer their ownership to other shareholders while generating a gain based on the valuation of the acquisition or IPO (Lerner and Willinge 2011). For example, MPM Capital, Pharmasset's venture capital backers for their series B round, shared their preference towards exiting via acquisitions, with MPM's founder Luke Evnin (2014) stating, "when we approach an investment, we really think about who's the buyer and what will we have to show that buyer? Is this a team and a product portfolio that will get us there?". In this way, venture capitalists are positioned between the state and financial markets of larger businesses and public shareholders. As Evnin (2014) continued in a blog post, "Due to NIH funding now also going towards programs that demonstrate commercial potential, our 'start ups' are much further along by the time we invest – even though they may still be straight out of academia." In the case of Pharmasset, venture capitalists viewed the company's hepatitis C assets – a product of the public funding described in the previous chapter – as a potential vehicle for generating financial gains.

This brings us to the second dynamic: these downstream financial markets placed a growing economic valuation – based on the anticipation of an increasing price and market size – on future hepatitis C assets. Using the library of compounds that Schinazi had developed in the 1990s with public support along with the newly developed replicon, Pharmasset's scientists embarked on testing potential nucleoside compounds for hepatitis C (Robbins-Roth 2001). By April of 2004, the company had identified a promising structure for a hepatitis C therapy, which they dubbed PSI-6130 (Furman, Otto, and Sofia 2011). The compound appeared to significantly

curtail the virus in rat populations, and would ultimately serve as the base structure for *sofosbuvir* (Furman et al. 2011).

The PSI-6130 compound for hepatitis C was a major driver behind Pharmasset's \$40 million venture capital series B round in October 2004 (Kallon 2010).¹¹⁸ The existing interferon-based therapies for hepatitis C were priced at ~\$36,000 per treatment regimen in 2004, yet only a small number of patients could take the treatment due to its toxicity (United States Senate, Committee on Finance 2015; Vernaz et al. 2016). In the US, only an estimated 50,000 patients annually began treatment, of the over 4 million infected (United States Senate, Committee on Finance 2015). Of these patients, only 15-40% responded to the treatment depending on the patient population, and most experienced significant side effects (Heim 2013). Patients waited until they were in the late stages of disease before taking the interferon regimen (Heim 2013).¹¹⁹ Investors anticipated that improvements in therapies could both command a higher price over time as well as translate to larger patient populations seeking earlier treatment of the disease. Pharmasset's SEC filing later at the time of their IPO captured this anticipation, in which they cited the past example of improvements in interferon treatment cure rates and increases in market value: "When the replacement of interferon with pegylated interferon in 2000 further increased the SVR rate to range of about 47% to 54%, sales of HCV drugs again increased significantly from more than \$1.3 billion in 2000 to more than \$2.0 billion in 2002" (Pharmasset 10-K 2007).¹²⁰ This expanding valuation of the 'market' – and the mobilization of venture capital into the innovation process – rested on an anticipation of prices for an improved therapy that would be some magnitude higher than the existing reference price.¹²¹ A recent retrospective evaluation found that launch prices for hepatitis C medicines indeed followed this logic, increasing over

¹¹⁸ Interviews 34, 35 reinforced this view, and was also represented in legal filings over the patent claims to PSI-6130 (Kallon 2010).

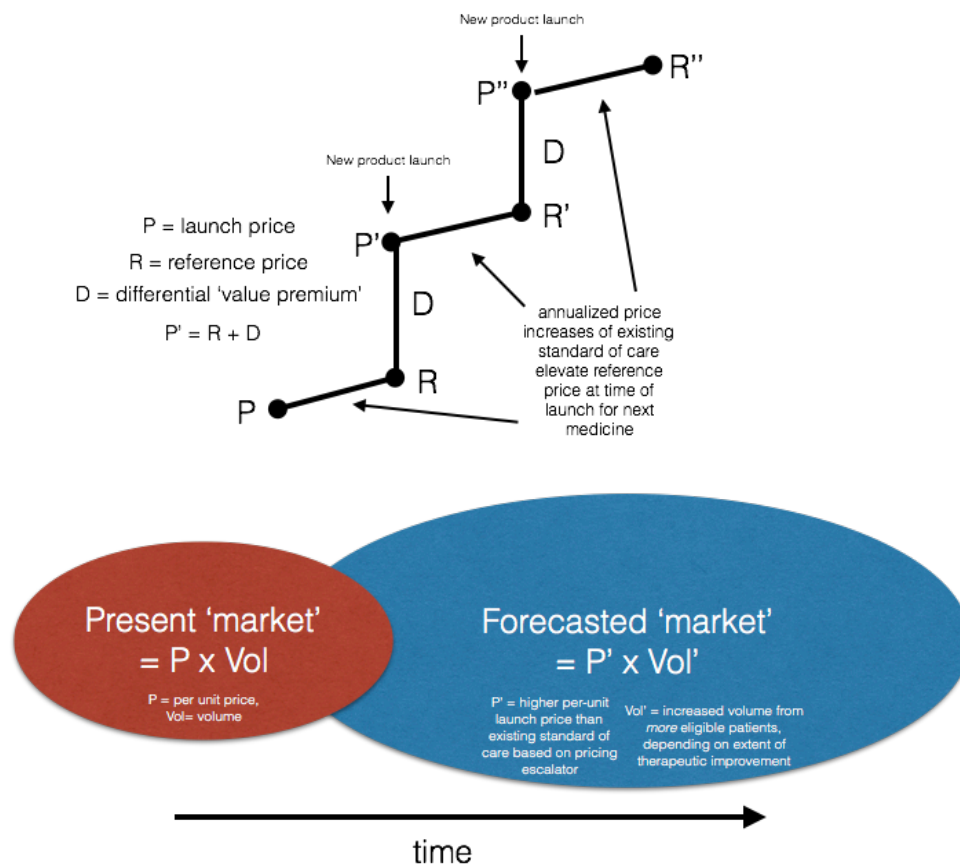
¹¹⁹ Interferon had first been tested in 1986, before the 1989 identification of hepatitis C (Hoofnagle et al. 1986). The NIH's Jay Hoofnagle, who had wondered if the therapy might work against non-A, non-B viral hepatitis, found that 11% of the patients experienced a cure after a year-long regimen (Hoofnagle et al. 1986b). Interferon would later be combined with ribavirin in improved formulations by Roche and Schering Plough in the late 1990s to yield better results, yet patients still experienced significant side effects and cure rates remained below 50% (Heim 2013).

¹²⁰ The 'replacement of interferon' with 'pegylated interferon' in 2002 represented an improvement at the time. As a reminder, SVR rate stands for 'sustained virologic response', and is equivalent to a cure.

¹²¹ This links back to the logic described earlier by the equation, Price = Value = Reference price + differential value (Maldonado Castañeda 2016). Here we see the function of such a pricing approach in speculative financial markets. I elaborate the emergence, uses, and consequences of the *pricing escalator* later in this chapter (sections 4.1.2 and 4.3 as well as in the next chapter, sections 5.1 and 5.2).

\$1,000 per 1% increase in cure rates for patients (Vernaz et al. 2016). I use the term *pricing escalator* to refer to this dynamic, which reappears throughout the chain of speculative capital that I trace later in this chapter (see Figure 4.1 for visual representation). In this way, investors were engaging in an intra-capitalist competition not just for profits but for *differential growth* (Cochrane 2011; Veblen 1908b).¹²²

Figure 4.1 Pricing escalator and expansion of market valuation



Note: Investors anticipated rising prices for future hepatitis C medicines based on buyers continuing to pay for higher prices for improved therapeutic outcomes in the future, with the price of the existing standard of care serving as a reference price (R) and an additional price (D) based on an estimate of the differential value of better health outcomes. Higher prices (R+D) combined with the larger volumes of patients who stand to benefit from a better medicine produced forecasts with expanding market valuations, the lure for speculative capital to make bets in the innovation process.

¹²² To put it another way, to garner further investment for hepatitis C compounds, investors bet that future market valuation (price x patient population) would be greater than the current market garnered by the capitalists that owned the approved therapies for hepatitis C at the time. This growth logic fueling larger market valuations lured capital behind Pharmasset.

The third dynamic follows from the first two: through the existence of these downstream financial markets as well as the potential for growing valuations, venture capitalists could pursue significant rewards from their investments while exiting far before the approval and sales of any medicine. Venture capitalists in biotechnology typically seek 40-75% rate of expected 'returns' on their investments (Lerner and Willinge 2011).¹²³ Such investors argue that this reward is warranted based on their relative illiquidity compared to downstream traders in stock markets (who can buy and sell shares on a daily basis) as well as the risks posed by unproven, early-stage businesses (Lerner and Willinge 2011). Furthermore, venture capitalists view themselves as 'active investors' who use their technical and business expertise and networks to take nascent businesses into potentially 'high value' businesses. Partners at venture capital funds with a biotechnology focus typically have a background in biomedical research and/or medicine which they use to evaluate potential technologies for investment that may otherwise fail to proceed (in terms of research and development) due to lack of financing. They also serve on the boards of investee firms, using their technical and financial expertise as well as authority as an investor to shape management decisions over talent, technology, and business strategy along the critical early stages of a firm's development (Robbins-Roth 2001, Booth and Salehidizah 2011, Hogarth 2017). Returns for venture capitalists are viewed in the light of this position as an 'active investor' in the innovation process as well as the expectation of making significant returns on successful investee firms to cover for the large proportion of failed investments.

An investment in any company with a particular hepatitis C asset contained some level of risk: while investors anticipated large and growing valuations for the overall hepatitis C market, a given compound could end up failing in clinical trials, thereby collapsing an investment. However, this risk was mitigated by the existence of financial markets through which venture capitalists (and downstream traders) could exit their ownership stakes far before the development of any compound. Pharmasset's venture capital investors, for example, each had a stake in the company from between three to eight years before Pharmasset's eventual public offering (S&P

¹²³ I have seen these estimates on expected returns vary, with one analyst putting the threshold at 400% returns for some venture funds (Glabau 2016b). The main point here is that venture capitalists seek returns far above the rates of return in the stock market due to the arguments cited above. An analysis of recent annualized returns between 2000 and 2010 of 1400 venture capital funds show that life sciences venture capitalists delivered 20% returns (higher than information technology), with skewed returns on successful deals covering losses on others (Booth and Salehizadeh 2012).

Capital IQ 2016b). From the IPO onwards, these venture capitalists exited their ownership stakes at variable points based on trading on Pharmasset's share price on the NASDAQ stock exchange.

In sum, the mobilization of venture capital into Pharmasset rested on 1) the opportunity to exploit publicly funded discoveries based on the existence of downstream financial markets that could 2) impute growing financial valuations to the hepatitis C market, thereby 3) enable the potential for significant gains at an exit far before the approval of any therapy for hepatitis C.¹²⁴

This mobilization of venture capital for the life sciences, however, was not a natural phenomenon, but a historically and politically constituted set of dynamics that coincided with technological and regulatory shifts in the 1970s and 1980s undertaken by the US state and influenced in part by new business interests. I highlighted the technological shifts in the previous chapter, in which advances of molecular biology – largely funded by the NIH – enabled scientists to pursue a much larger array of technical directions (Vallas et al. 2011). The expansion of venture capital to commercialize the developments made possible through these publicly funded discoveries rested in two further sets of regulatory changes. The first set of changes related to the conversion of public into private intangible assets, which I also documented in the prior chapter, regarding the Bayh-Dole Act as well as other related changes to commercializing knowledge during the 1980s (Rai and Eisenberg 2002). This enabled a political-legal apparatus via which smaller spin-off enterprises like Pharmasset became vehicles for venture capital investment.

The second set of US regulatory shifts relates to the structure of financial incentives and flow for venture capital in the late 1970s into the 1980s. Two principal changes occurred. First, in 1979, the Department of Labor amended the Employment Retirement Income Security Act of 1974's (ERISA) "prudent man rule", which had previously prevented pension funds from investing substantial sums in venture capital funds or other 'high-risk' asset classes (Gompers 1994; Lazonick and Mazzucato 2013). Through their amendment, the Department of Labor instead allowed pension funds to invest up to 10% in venture capital (Gompers 1994). A second rule change had come the year before, when the emerging high tech and venture capital trade

¹²⁴ Venture capital for hepatitis C followed the broader pattern indicated by Pharmasset: entering in after the advent of the replicon, venture funds sought to make gains not from the profits of any newly approved medicines – no new classes of medicines were approved for hepatitis C until 2011 – but from the potential to make gains in speculative financial markets. Between 2004 and 2008, the industry group BIO estimated that venture capital funds invested \$500 million in *all hepatitis C projects* led by small biotechnology companies {Thomas:2015wq}. In the period between 2008 and 2012, however, this figure dropped to \$101 million, with fewer new companies pursuing hepatitis C once compound had moved into later stage clinical trials and larger companies had acquired venture-backed businesses with hepatitis C assets {Thomas:2015wq}.

associations successfully lobbied the US Congress to decrease the capital gains tax from 49.5% to 28%, as they viewed this to be an additional incentive to draw in venture capital (Gompers 1994). The ascent of venture capital proved significant in the decade following these two regulatory changes: in 1978, before these regulatory and tax changes, venture capital amounted to a small slice of economic activity, with a total of \$216 million in commitments to such funds (Gompers 1994). Pension funds made only 15% of this commitment. By 1988, pension funds accounted for nearly half of a total of \$3 billion committed to venture capital funds (Gompers 1994). Taken together, therefore, these shifts helped produce an expansion of venture-backed biotechnology companies.

In this section, I have illustrated the function of venture capital for Pharmasset and the innovation process behind *sofosbuvir* as well the pricing and valuation strategies underpinning the circulation of this capital. Furthermore, I have shown that critical shifts mobilized by the US state in the 1970s and 1980s enabled the emergence of this form of capital. Rather than pursuing the financing of drugs through to their approval, venture capital mobilized on the basis of downstream financial markets valuing hepatitis C assets and enabling a significant reward at a time of a pre-approval exit from their ownership stakes. In this way, the venture capital behind Pharmasset became one link in a longer chain of multiple speculative capitals. We continue our tracing of this chain of capitals onwards into the next section.

Table 4.2: Venture capital rounds financing Pharmasset, 1998-2004

Round of funding	Date(s)	Amount / Deal	Venture capital investors
Series A (seed funding)	1998-1999	Precise number unreported; likely ~2.5 million ¹²⁵	\$ 1 million from Idenix (originally called Novirio) in exchange for 1 million shares; 1 million from Microbiologica, a Brazilian manufacturer led by Dr. Jaime Rabi; ~\$500K from family and friends
Series B	June 1999	\$3.91 million / 2.3 mil shares at \$1.70 per share	MPM Capital (BB BioVentures LP) *Ansbert Gadick of MPM joined company's board
Series C	February 2001	\$7.4 million / 1,357,798 shares at \$5.45 per share	TVM Capital (KG) *Alexandra Goll, partner at TVM Capital joined company's board
Series D	August 4, 2004	\$40 million / 7,843,380 shares of series D redeemable convertible preferred stock at \$5.10	Burrill & Company *G. Steven Burrill, Founder and Chief Executive Officer of Burrill & Company joined the company's board of directors.
		Total venture funding \$53.81 million	

Source: Pharmasset's S&P Capital IQ report (2016b)

Table 4.3 Summary of venture capital funds behind Pharmasset

Venture fund	Key facts about venture fund	Pharmasset investment and period to IPO
MPM Capital	<ul style="list-style-type: none"> - Founded in 1997, based in Boston - 23 deals - \$2 billion in management, split 80/20 on drug development and medical device ventures 	<ul style="list-style-type: none"> - Led series B round in 1999 for \$3.91 million - 8-year investment period, from 1999 to 2007
TVM Capital	<ul style="list-style-type: none"> - Founded in 1983 as one of the first venture capital funds in Germany - 37 deals, 8 exits - Focuses on information technology as well as biotechnology 	<ul style="list-style-type: none"> - Led series C round in 2001 for \$7.4 million - 6-year investment period, from 2001 to 2007
Burrill and company	<ul style="list-style-type: none"> - Founded in 1985, based in San Francisco - 15 deals - Focused almost exclusively on life sciences with some investments in agriculture and biomaterials 	<ul style="list-style-type: none"> - Led series D round in 2004 for \$40 million - 3-year investment period by IPO

Source: FierceBiotech profiles

¹²⁵ From personal correspondence with Pharmasset co-founder and reiterated in Atlanta Business Chronicle story (Robbins 1999).

4.1.2 A financial market of pharmaceutical assets: a corporate partnership and an IPO

Beyond initial public funding and venture capital, Pharmasset's leadership searched for further financing to sustain the long-term research efforts required to develop new therapies. As the prior section highlighted, venture capital would only provide partial financing, and with a structural preference and positioning oriented around an 'exit' in which they pass ownership to other investors. To sustain their research efforts, Pharmasset turned to two kinds of actors: a larger pharmaceutical business in Roche, and public equity markets through an IPO. Both directions financed Pharmasset's search for compounds in the near-term, and like venture capital, rested on pricing and valuation strategies that bet on growing markets and prices for hepatitis C assets as well as short-term exits.

By the spring of 2004, Pharmasset had what it viewed to be a promising pharmaceutical asset in PSI-6130 (Kallon 2010). The company had decided to advance the compound into early human trials, as PSI-6130 had shown profound inhibition of the virus via binding to its NS5b polymerase protein both in the replicon and subsequently with rats (Furman et al. 2011). Though Pharmasset aimed to pursue this nucleoside strategy further, many questions typical of pre-clinical drug development remained: how long would the compound stay in the body? How much of the compound would be needed for the desired effect? Would the compound be safe in humans? Questions of potency, effectiveness, and toxicity hung over the future of the compound. With no experience in hepatitis C clinical trials, Pharmasset looked to a strategy that had grown in the past two decades in the biotechnology and pharmaceutical sector: the 'strategic partnership' between small enterprises and established companies (Bartenschlager et al. 2016; Sofia et al. 2010).

Strategic partnerships have been pursued within the industry as a way of joining up the supposed comparative advantages of small and large companies, with small biotechnology companies supplying established businesses with compounds from early stage research often deemed to be too risky for larger firms, and larger businesses providing clinical trial expertise to small companies with little expertise in the development process (Pisano 2006).¹²⁶ In the past

¹²⁶ While venture capital provides financing to the overall business, capital from established pharmaceutical companies typically focus on advancing a specific pharmaceutical asset onwards into clinical trials (Baum et al. 2010). This approach can be thought of as project-based financing. Some venture investments emulate this focus, especially for businesses working on single therapeutic classes, for example.

three decades, such alliances have grown as a mode of interaction between small and large companies, especially as large companies have outsourced early stage research.¹²⁷

Just months after closing their series D round and patenting their PSI-6130 compound, Pharmasset struck such a ‘partnership’ deal with Roche, a large Swiss-based pharmaceutical company (Roche 2004). As the manufacturer of the leading hepatitis C treatments at the time, *interferon*-based treatments Pegasys and Copegus, Roche saw potential in Pharmasset’s PSI-6130 compound to expand their anti-viral strategy (Roche 2004). Roche’s *interferon* treatments were toxic and many patients avoided taking them until their disease had already progressed into its later stages (Heim 2013). Their public list price for the regimen was about \$40,000, and the market for hepatitis C – which also included Schering Plough’s *interferon* products – had grown to over \$2 billion in sales by 2004 (United States Senate, Committee on Finance 2015). Much like Pharmasset’s venture capital backers, Roche hoped that progressive improvements in treatment, such as by pairing *interferon* with a compound like PSI-6130, could enable them to grow the potential pool of patients who might start the regimen at earlier stages of the disease.

With recent expertise in hepatitis C clinical trials with their *interferon* regimens, Roche aimed to conduct further investigations into the efficacy and safety of Pharmasset’s compound in humans. The deal called for Roche to make an up-front payment of \$8 million to Pharmasset, with Roche agreeing to further pay upwards of \$105 million in milestone payments if the compound made it through to advanced clinical trials, and royalty payments on any approved products. In exchange, Roche would gain global rights for the compound and accrue all associated revenue, minus the royalty payments to Pharmasset (Pharmasset 2006). Finally, Roche also gained share equity in Pharmasset in the form of ‘convertible stocks’ that could turn into common stocks should the company go for an initial public offering (IPO); this share equity element in their agreement mitigated Roche’s risk by assuring them of a potential near-term gain should the PSI-6130 compound not make its way to approval and sales (Pharmasset 2006). Over the next six years during which the two companies partnered on clinical trials for PSI-6130 and its modified

¹²⁷ The effectiveness of strategic partnerships for generating innovation has been contested due to the short time horizons and secrecy involved between firms attempting to share knowledge about assets, both of which eschew the long-term learning required for drug development (Danzon, Nicholson, and Pereira 2005; Gleadle et al. 2014; Pisano 2006). I do not engage in the debate over this division of labor here, but provide this context to situate Pharmasset’s strategy.

versions, Roche directed \$44.5 million to Pharmasset (Pharmasset 2011).¹²⁸ In turn, Roche received 266,667 shares in Pharmasset at the time of its IPO at a value of \$2.4 million (Pharmasset 2009). As Roche continued with clinical trials during the mid into late 2000s, Pharmasset took this capital to pursue compounds both in hepatitis C as well as HIV and hepatitis B. Yet they would also turn to another set of financial actors to sustain their research and development efforts: public shareholders.

By 2006, Pharmasset began to prepare for an initial public offering (IPO), converting it from a privately held company to one that would be publicly traded on the NASDAQ stock exchange (Robbins-Roth 2001). Two factors shaped Pharmasset's move: first, an IPO would enable Pharmasset's venture capital investors to exit and "cash out", and second, the offering could generate a new round of capital to finance the company's clinical trial efforts. At the stage of the IPO, institutional shareholders enter into the innovation process in a more direct manner (up to this point, their role has been the indirect, via the financing of venture capital funds), as they take ownership from VC funds and then pass ownership on to other shareholders (Andersson et al. 2010; Hopkins et al. 2013). Hopkins et al (2013:909) have argued that institutional investors at this stage can be seen less as processing physical materials and more as "pipelines that process financial contracts". Rather than provide capital for the remainder of the innovation process, institutional investors and the IPO process create a market for speculative trading in which equity investors can move in and out of their investment in a particular company. The 'market price' created by the IPO valuation process enables these exchanges, by which traders aim to pursue capital gains.¹²⁹

Such trading in pharmaceutical assets – many of which may never receive regulatory approval and generate earnings – has been facilitated through the specific configuration of the NASDAQ stock exchange. As described by Lazonick and Mazzucato (2013), the NASDAQ exchange, unlike its older New York Stock Exchange (NYSE) sibling, allows companies like Pharmasset with no record of profits and low capitalization to do an IPO. Like the formation of

¹²⁸ Roche eventually abandoned further development of PSI-6130 (called RG-2748 at Roche) in 2011, after other companies (like Pharmasset itself with *sofosbuvir*) came to Phase II and Phase III trials with compounds that had an advantage in clinical outcomes and dosage (Pharmasset 2011).

¹²⁹ Multiple observers have pointed to the tendency of such speculative equity markets, with a small number of institutional investors concentrating share ownership, to become riven by short-termism, herd behavior, and risk aversion (Haldane 2011; Hopkins et al. 2013; Lazonick 2015). While I do not provide an exhaustive analysis of this short-termism, I describe how it operates in the context of larger pharmaceutical companies later in the chapter.

venture capital, NASDAQ was also a product in part of the US state: the exchange was created in 1971 as the world's first electronic stock market upon the encouragement and guidance of the US Securities and Exchange Commission.¹³⁰ The presence of NASDAQ allowed for a highly liquid financial market via which venture capitalists could exit their initial investments (Lazonick and Mazzucato 2013). Traders could enter and exit based on fluctuations in the share price, which were in turn shaped by development milestones and clinical trial results of intangible pharmaceutical assets, rather than forecasts of profitability and earnings.

Pharmasset raised \$45 million via its IPO on April 26, 2007 on the NASDAQ exchange, with their stock trading at \$9 per share (Reuters 2007). Of the \$45 million raised by Pharmasset, four institutional shareholders each held more than 5% of the company's shares (S&P Capital IQ 2016b).¹³¹ This valuation was based on Pharmasset's focus on three clinical trial stage nucleoside compounds including the PSI-6130 compound being developed with Roche as well as one for hepatitis B (clevudine) and HIV (racivir) (Pharmasset 2006; 2010; Reuters 2007). For each compound, Pharmasset forecasted the potential for major revenue. As I highlighted earlier with the phenomenon of the 'pricing escalator', Pharmasset had observed that even modest improvements in treatment had led to increases in revenue in the past. The company predicted that worldwide sales for anti-virals against hepatitis C would go from \$2.2 billion in 2005 upwards to \$4 billion by 2010 and \$8 billion in 2015 (Pharmasset 2006; 2010; 2011). With 15 million chronically infected with hepatitis C in the major markets of the US, Europe and Japan, Pharmasset's senior leadership believed their development program for hepatitis C could generate the compounds to gain a share of that future growth.

Shareholders bet on this promise as well. As Pharmasset patented a compound believed to hold breakthrough potential in 2008 and began to run clinical trials showing promising results in 2010 and 2011, the company raised further capital in the public equity markets by issuing new shares – with five separate rounds of 'follow-on' financing amounting to \$345.9 million in capital

¹³⁰ After a 1963 report submitted to the US Congress on a study of securities markets, the SEC recommended that the National Association of Security Dealers (a private body of security traders overseeing the trading activities of its members) make use of new computer technologies to establish a national electronic quotation system for what are known as 'over the counter stocks' – or stocks that traded off the main stock exchanges (Lazonick and Mazzucato 2013).

¹³¹ The major institutional shareholders – both pension funds as well as hedge funds – at the time of Pharmasset's IPO were the following (S&P Capital IQ 2016b): Fidelity Management and Research (467,800 shares for \$4.552 million), T Rowe Price (75,000 shares for \$729,750), QVT Financial 2,055,498 shares for \$20 million), and BlackRock Advisors (275,000 shares for \$2.675 million).

(S&P Capital IQ 2016b). Pharmasset used a fraction of this capital on research and development, which focused on clinical trials in 2010 and 2011 for the compound that would ultimately be *sofosbuvir* (spending \$124.1 million) (Pharmasset 2011:66). These ‘follow-on’ financings also enabled new shareholders to trade on Pharmasset’s rising price: the price of Pharmasset’s shares ascended in 2010 and 2011 – reaching \$85 dollars per share in October of 2011 on the strength of this potentially breakthrough therapy (Carroll 2011; Feuerstein 2011). We turn to the development of this breakthrough next.

4.1.3 *Sofosbuvir* as a hybrid breakthrough: public science meets private asset

While Pharmasset relied on the mobilization of this speculative venture and public shareholder capital for its financing at this stage, the company’s breakthrough would rest in the application of publicly funded science generated a decade before. The PSI-6130 compound, the centerpiece of their hepatitis C strategy and their partnership with Roche, suffered from a central limitation: when the compound entered the blood circulation, it metamorphosed into multiple different chemical versions, reducing its overall potency in the liver (Furman et al. 2011; Gounder 2013; Sofia and Furman 2010). This chemical dis-banding limited its effectiveness in eliminating the virus from the liver, thereby requiring multiple pills, increased dosages, and the potential for greater side effects. While Roche continued their attempts to improve the drug as it proceeded into clinical trials, Pharmasset’s own scientists pursued research into other potential hepatitis C compounds. One of these scientists, Michael Sofia, had examined the PSI-6130 effort and began searching for an alternative direction based on several looming questions (Sofia and Furman 2010): was it possible to reduce the pill count, lower the dosage, and increase the potency of the compound even further than PSI-6130 could? The PSI-6130 compound would provide a therapeutic benefit, but not to the extent that would jettison interferon from treatment regimens. A more potent compound could reduce or eliminate the need for the toxic *interferon* altogether, which would dramatically increase the numbers of patients who might benefit from treatment (Sofia and Furman 2010).

To build a compound that transcended PSI-6130’s limitations, Sofia and his team at Pharmasset looked to an innovation from European scientists. The origins of PSI-6130’s limitations were known: the compound suffered from an diminished ability to complete a set of modification steps once in the blood stream (Sofia et al. 2010). Blocked at an earlier step, the compound transmuted into its inactive version, thereby reducing its potency. Sofia surmised that

bypassing this blocked step would hold the key to boosting any approach to inhibiting its target, the virus's NS5b polymerase (Bartenschlager et al. 2016). In his search for potential bypass strategies, he encountered the work of a British scientist, Christopher McGuigan. In the 'McGuigan method', an additional chemical structure called a 'phosphoramidate' is added to a base compound, with this structure serving as a 'mask' until it reached the liver (Cardiff University 2014; McGuigan et al. 2010; Perrone et al. 2007). By adding the 'mask', Sofia aimed for the body to take advantage of its own physiology: because the liver is often the first place where a drug is absorbed and modified, Sofia hypothesized that the mask would fall off in the liver, thereby revealing the chemical structure ready to undergo the necessary modification steps to bind and inhibit the NS5b polymerase (Gounder 2013). Sofia believed he had found his Trojan horse. By sneaking into the liver with a mask, the compound would have its greatest effect in precisely the organ where hepatitis C was wreaking its damage.

McGuigan had pioneered this method in collaboration with Belgium scientist, Jan Balzarini, over the prior decade (Balzarini et al. 1996; McGuigan et al. 1996b; Mehellou et al. 2009). Based at Cardiff University in the UK, McGuigan led the effort to develop this phosphoramidate structure and method, first in the context of HIV and then other viruses (like hepatitis C) and more recently in cancers (McGuigan et al. 2010). In the seminal 1996 paper describing the approach McGuigan and his collaborators cited four public sources of funding: the British Medical Research Council, two programs of the European Commission, and the Belgian government.¹³² A subsequent paper in 1999 reiterated these funding sources (Siddiqui et al. 1999).¹³³

Accessing this knowledge through the public domain, Sofia was able to apply it to Pharmasset's hepatitis C research (Cardiff University 2014). Attempting multiple versions of the phosphoramidate "mask" and fixing it onto the base PSI-6130 structure, Sofia finally found one iteration which showed a profound decline in the virus (Bartenschlager et al. 2016; Sofia et al. 2010). Additionally, the modified inactive versions that had been observed with the PSI-6130 were absent. The new structure would be named PSI-7977, and eventually receive the name *sofosbuvir*.

¹³² The precise funding sources named were The AIDS Directed Programme of the MRC, the Biomedical Research Programme and the Human Capital and Mobility Programme of the European Commission, the Belgian Geconcerteerde Onderzoeksacties, and the Belgian Nationaal Fonds voor Wetenschappelijk Onderzoek. See McGuigan (1996, 1999) papers for more.

¹³³ I could not locate the precise figures for this funding, as specific grants were not identified; these grants pre-dated internet databases that have archived this type of information for the public.

after its lead scientist. PSI-7977 became Pharmasset's lead candidate for hepatitis C in 2008, after a three year period of pre-clinical testing by Sofia and his team. Documenting this process in chemistry and medical journals after the development of *sofosbuvir*, Sofia cited the McGuigan method as the pivotal and defining step to arrive at the curative backbone compound (Bartenschlager et al. 2016; Sofia and Furman 2010; Sofia et al. 2010).¹³⁴

The *sofosbuvir* structure and curative function can be observed to be a hybrid public-private outcome, recombining publicly funded knowledge in the context of a publicly-traded business (see Figure 4.2 for hybrid genesis of *sofosbuvir*). Pharmasset filed for intellectual property protection on this new compound in 2008,¹³⁵ and began to prepare for early stage human trials in 2009 and 2010 (World Health Organization 2016). By 2008 Pharmasset had developed more clinical trial capabilities, having attempted to develop compounds in HIV and hepatitis B in the previous half-decade and worked in partnership with Roche on its hepatitis C protocol (Pharmasset 2009; 2010). With this experience and the requisite financing from their IPO, Pharmasset pursued early Phase I and Phase II clinical trials as an independent company (Pharmasset 2011). Over the course of these two years, Sofia's application of the McGuigan method would be validated in several Pharmasset-led early-stage clinical trials, with each trial showing promising results (Gounder 2013; Knight 2013).

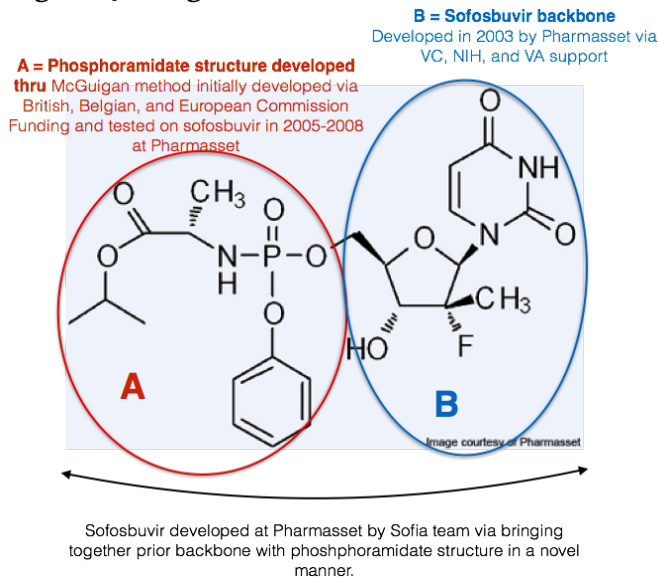
Though in small samples, the compound showed results heretofore not witnessed in hepatitis C: in Phase II trials for example, *sofosbuvir* cured hepatitis C in rates higher than 90% in multiple cohorts among a 564-patient population (Pharmasset 2009; 2010). Pharmasset used the capital generated from its IPO as well as further secondary financings from shareholders to run these trials at a total cost of \$62.4 million. To further validate their compound, Pharmasset worked with the National Institutes of Health on a Phase II trial in the sickest patient populations often under-represented in clinical trials for hepatitis C by private companies: African Americans

¹³⁴ In one of his papers aimed at more public medical audiences written with other hepatitis C scientists, Sofia (2016) described their overall strategy, "To address the deficiencies of the PSI-6130 prodrug a radical redesign of this nucleoside inhibitor was developed by Sofia and colleagues [...] To address the problem of delivering a highly charged, unstable, and membrane-impermeable uridine monophosphate into cells and ultimately into the body, a 'Trojan horse' strategy was developed that masked the uridine monophosphate in such a way as to impart stability and facilitate transport into the body and into liver cells." In another of his papers, Sofia (2010) described the source of their Trojan horse strategy: "We speculated that application of the phosphoramidate prodrug method would be an ideal approach for delivering the desired uridine monophosphate to hepatocytes in an in vivo setting." Here the McGuigan method is called the 'phosphoramidate prodrug method'.

¹³⁵ Roche, Merck, and AbbVie would all later sue Gilead over *sofosbuvir*'s patents.

and those with advanced liver disease (Osinusi et al 2013).¹³⁶ In case they chose to remain a free-standing company, Pharmasset meanwhile also plotted out \$90.4 million to bring the compound all the way through Phase III trials and registration with regulatory authorities (United States Senate, Committee on Finance 2015).¹³⁷

Figure 4.2 Organizational and financial sources of sofosbuvir structure



Note: Sofosbuvir structure is composed of the phosphoramidate component developed through public European sources along with the backbone developed at Pharmasset, itself supported by a mix of private and public funding at the time of its discovery. VC = venture capital.

Table 4.4 Phase I and Phase II clinical trials for sofosbuvir by Pharmasset and NIH

Trial	Time period	Patients tested
Phase Ia / Ib	June 2009	Tested safety and tolerability in healthy patients (Ia), and then in chronically infected patients (Ib)
Phase IIa / IIb (3 trials) - ELECTRON - POSITRON - ATOMIC	2010-2011	564 patients across different populations and regimen lengths
Phase II trial (National Institutes of Health)	2011-2013	60 patients, under-represented and sicker patients not otherwise tested (African Americans, advanced liver disease)

See Table 4.6 for total costs of sofosbuvir development, including pre-clinical research as well as clinical trial development by Pharmasset and Gilead Sciences. Sources: Pharmasset SEC 10-K and Gilead Sciences 10-K filings.

¹³⁶ The NIH sponsored the trial, releasing data with positive findings in mid-2013.

¹³⁷ See Table 4.6 later in the chapter with a breakdown of these reported costs.

4.1.4 Potential pathways for Pharmasset: durability or disposability?

As Pharmasset entered 2011 with PSI-7977 looking to be a potent intangible asset, the company's senior leadership had a decision to make, typical of small biotechnology companies with compounds preparing for later stage trials: to grow as a durable, free-standing business, or become a 'disposable' business via an acquisition by an established pharmaceutical company (Baum et al. 2010; Ozmel et al. 2013). Documents from Pharmasset's strategic planning and board meetings captured by the US Senate investigation reveal that two major considerations shaped the company's self-assessment about its future: first, the timing and results of further clinical data for PSI-7977 and competing compounds, and second, their capability to grow into a diversified, global enterprise.

If Pharmasset were to find a partner or get acquired, they wanted it to be with the right company for the right price. Early indications from their Phase II trials were that PSI-7977 would work most effectively if paired with a second compound, much like combination therapies for HIV (Garber 2011). Using PSI-7977 alone as a 'mono-therapy' could otherwise lead to high rates of resistance and lower cure rates (Sofia et al. 2010). Several established companies, such as Bristol Myers Squibb, Gilead Sciences and Merck, had developed compounds that might work in tandem with PSI-7977, but the data on those compounds still presented a murky picture, as few had made it into later-stage clinical trials (Garber 2011). Pharmasset knew they could gain leverage by waiting (Flinn 2011). With complete Phase II trials for PSI-7977 to be released in late 2011, the compound would likely be in high demand; none of the larger companies had developed a backbone compound with its potency (Flinn 2011). Furthermore, if Pharmasset chose to pursue another partnership like it had done with Roche previously, choosing the company with the right 'partner compound' for PSI-7977 would be pivotal. If the right combination were not chosen, Pharmasset would not only lose out on future revenues from the compound, but also the opportunity to get out-right acquired. With these possibilities in mind, they proceeded with caution (United States Senate, Committee on Finance 2015:645):

"At this point in time, the likelihood of choosing wrong is significantly higher than the likelihood of choosing the right combination partner for PSI-7977. As an example, assume that a protease inhibitor is the correct combination partner. [...] There is only a 15% overall probability of choosing the correct compound for combination with PSI-7977 and achieving the Good Deal scenario."

Pharmasset's "15% overall probability" came from their analysis of the compounds they saw in the hepatitis C market, many of which had yet to proceed into Phase II trials. By waiting, Pharmasset would gain more information with which to determine any decisive steps towards the right deal. In the meantime, Pharmasset's executives evaluated whether they could build a durable free-standing business.

But to grow as a standalone company, Pharmasset forecast the challenge of building a global marketing, regulatory, and distribution networks that would require new expertise and financial resources that they currently did not have (United States Senate, Committee on Finance 2015:502). Additionally, Pharmasset worried that they would need to quickly diversify to other areas of therapeutic development after the launch of PSI-7977, as a curative therapy for hepatitis C would not lead to the type of continuous growth that their shareholders expected. The company's viability as a single-product business remained a looming question, and the team began to explore other therapeutic areas it could enter.¹³⁸ They later concluded that the prospects for diversification would need to come from outside the company. "In fact, given the substantial time frame from research program initiation to product launch," Pharmasset's leaders observed in a 2011 board meeting update, "it is highly unlikely that any *de novo* research program will provide the necessary revenue in the required timeframe" to deliver growth beyond hepatitis C (United States Senate, Committee on Finance 2015:501). In this context, larger companies appeared to be better suited to be Pharmasset's suitors in a potential acquisition than as competitors vying for growth (Garber 2011).

Which path would *sofosbuvir* take in the hands of Pharmasset? As observed in section 4.1, the promise of escalating market valuation and growth had circulated a chain of speculative capital into the innovation process behind *sofosbuvir*, with the cash hungry and deficit-running Pharmasset entirely reliant on external capital markets for financing as the drug development process moved forward. Understanding its next steps in the innovation process thus demands an analysis of another set of financial dynamics alongside those of speculative asset-based markets: the relationship between shareholders of large pharmaceutical businesses and the corporate

¹³⁸ In a July 2010 board meeting memorandum, the company highlighted its challenge due to failures in HIV and hepatitis B, and attempted to plan a response: "Pharmasset no longer possesses such a well-balanced pipeline. Presently, Pharmasset's pipeline is entirely focused on nucleoside analogs for treating HCV [...]. However, over time, we have identified opportunities that with a little investment in research could result in success in several years" (United States Senate, Committee on Finance 2015:646)

strategies of these businesses, and in turn the relationship between large and small biotechnology companies.

4.2 Life science or shareholder science? Gilead's position in the innovation process

As Pharmasset scanned the future for its options entering into 2011, large established pharmaceutical companies viewed the hepatitis C market with anxiety and promise: the growing valuation of the market indicated the significant financial potential, yet none of the major companies appeared to possess the compounds and treatment regimen to accrue the large share of these potential earnings (Garber 2011; Knight 2013; Rice and Saeed 2014). One of these large, publicly traded companies was Gilead, which found itself in a predicament by the summer of 2011: beyond their HIV/AIDS medicines, research and development efforts within the company bore few fruits during the 2000s. The scope for further growth seemed limited: to many Wall Street analysts, Gilead appeared destined to be a single disease business (Jannarone 2011). Though improved treatments for hepatitis C presented a new revenue opportunity, Gilead found itself stuck (Jannarone 2011). When Pharmasset surveyed Gilead's history in a strategy document, they noted: "Today (2011) Gilead is left wondering what to do in HCV," due to a "lack of successes" (United States Senate, Committee on Finance 2015:665).

In section 4.2, I trace Gilead from its genesis to its position in the hepatitis C innovation process in 2011 to reveal the mechanisms by which shareholders controlled the company's capital allocation strategies. Unpacking the 'shareholder growth treadmill' – the near-term and differential growth demanded by shareholders – faced by companies in publicly traded financial markets, I show how Gilead was exposed to a structural crisis in 2011 that explains its position in the innovation process less as a research and development company, but as an accumulation center – using accumulated capital from prior sales to specialize in acquisitions of late-stage assets in the drug making process.¹³⁹ This section thus introduces the extractive logics driving Gilead's shareholders and the ways this influenced the innovation process behind *sofosbuvir*.¹⁴⁰

¹³⁹ This analysis in turn situates Gilead's pursuit to acquire Pharmasset as described in the following section.

¹⁴⁰ I elaborate on these logics later in the chapter as well as in chapter 5, before synthesizing its implications for the *sofosbuvir* process in the discussion chapter (chapter 6).

4.2.1 Gilead's rise: acquiring and recombining innovations for HIV/AIDS

From its early origins onwards, Gilead's business strategy has centered on acquiring pharmaceutical assets from outside the company and then *recombining* them into treatment regimens that could be used in a larger patient population than each individual compound could otherwise on their own.

Launched in 1987 by a medicine and business graduate, Michael Riordan, Gilead initially focused on a new biotechnology (anti-sense technology) that could be used to shut down proteins responsible for viral replication (Brown 1997). Unlike Pharmasset, the company did not emerge from a publicly funded lab at a university, but rather materialized in Silicon Valley during the early years of biotechnology with a growing abundance of speculative capital to finance new ventures (Chandran et al. 2014). The company began with \$6 million in venture capital (Brown 1997). With no products or profits, Gilead went public in 1992 on the NASDAQ exchange, raising \$86.25 million with 5.75 million shares of common stock in its initial public offering (IPO) (Brown 1997). By then, the company had shifted from its initial anti-sense strategy, as it attracted capital based on an approach of finding compounds from outside the company (Rangan and Lee 2009).

Under the leadership of John Martin, a medical chemist recruited from Bristol Myers-Squibb with experience in anti-viral research, Gilead turned its focus to nucleoside science. Martin envisioned a two-pronged business model: 'in-licensing' compounds from other companies and institutions while also attempting to build up its internal research capabilities (Rangan and Lee 2009). For example, Gilead in-licensed compounds from researchers at two institutes in Europe with whom Martin had worked while at BMS.¹⁴¹ One of these compounds – *tenofovir disoproxil fumarate (TDF)* – would be approved in treatment for HIV in 2001, becoming the only once-daily pill at the time (Rangan and Lee 2009). After a minor acquisition in 1999 of the company NeXstar, Gilead's second purchase in 2003, Triangle Pharmaceuticals, poised the company for dominance in HIV/AIDS (Gilead Sciences 2016a). For \$464 million, Gilead gained ownership of a compound known as *emtricitabine*, which had already received FDA approval (Gilead Sciences 2016a). Ray Schinazi, also the founder of Pharmasset, had begun Triangle in 1996 based on developing *emtricitabine* (Cohen 2015). With these two compounds – *TDF* and

¹⁴¹ In 1991 and 1992, Gilead entered into "royalty" agreements with the institutions where his European colleagues had worked: the Institute of Organic Chemistry and Biochemistry at the Academy of Sciences of the Czech Republic (IOCB) and the Rega Institute for Medical Research, Katholic University in Leuven, Belgium (Rangan and Lee 2009). The agreements specified that the institutions would receive royalty payments if compounds led to a marketed product.

embtricitabine – Gilead bet on a strategy of recombining innovations from outside the company to realize commercial success.

Within three years of its acquisition of Triangle, Gilead offered two main treatments for HIV/AIDS: first Truvada, launched in 2004, and then Atripla, launched in 2006. Truvada was a combination of *embtricitabine* and *TDF*, while Atripla added a third compound licensed from Merck (Rangan and Lee 2009). Before this point, patients with HIV/AIDS typically required multiple medications taken multiple times a day, making it difficult to adhere to treatment and increasing the likelihood of side effects. Combining multiple medicines into a once-daily treatment, as Truvada and Atripla did, allowed Gilead to become the leading manufacturer of HIV medicines. Though five classes of medicines existed for HIV, with 20 different anti-retroviral compounds, 80% of patients in the U.S. by 2008 received one of Gilead's HIV medicines (Rangan and Lee 2009).¹⁴² From its launch in 2004 to the end of 2011, Truvada generated \$13.5 billion in total revenue (Gilead Sciences 2012). Atripla amassed \$11.2 billion by 2011, surpassing Truvada in yearly sales in 2010 (Gilead Sciences 2012). Gilead's HIV strategy had paid off, leading the company to grow during the 2000s from a small publicly traded company with no products and sales to a growing biopharmaceutical company generating \$8 billion in revenue by 2011.

Gilead's strategy thus rested less in scientific discovery within their labs and more in recombining discovery from beyond its Foster City campus (Rangan and Lee 2009). Both *TDF* and *embtricitabine*, the backbone compounds in their HIV regimens, came from university laboratories, with Gilead making modifications and then bringing them together in single pills for simplified treatment regimens (Rangan and Lee 2009). Yet Gilead's acquisition-based strategy was positioned to respond to a structural crisis driven by the expectations and influence of Gilead's shareholders. Understanding the financial stakes for Gilead in the summer of 2011 provides insight into the structure of this crisis.

¹⁴² Though the majority of patients received either Atripla or Truvada, a smaller percentage also received *embtricitabine* (brand name: Embtriva) and *TDF* (brand name: Viread) in combination with therapies from other companies, with Gilead receiving a portion of those sales.

Box 4.1 Gilead by 2011: key primer facts

- Founded in 1987 by Michael Riordan, IPO for \$86.25 million with final share-financed capital investment coming in 1996
- Major HIV compounds *TDF* (licensed in 1996) and *emtricitabine* (acquired in 2004) from university labs via licensing and acquisition, respectively. Both compounds are the backbone in their HIV combination therapies Truvada and Atripla.
- HIV regimens amounted to \$33 billion in sales in the decade between their launch in 2001 and 2011, with annual sales of over \$7 billion in 2011 (representing 90% of the company's total revenue)

4.2.2 Gilead's structural crisis: the shareholder growth treadmill, patent cliffs, and a dry pipeline

In the years between 2009 and 2011, Gilead's rates of profitability were considerable, ranging from 33% to 37.6% (Gilead Sciences 2012).¹⁴³ For Gilead, this rate of profitability was possible due to its patent protected prices and revenues in a single therapeutic area: medicines for HIV/AIDS. This singular product focus, built on the licensing and acquisitions of *TDF* and *emtricitabine* highlighted in the previous section, generated almost all the company's revenue during the previous decade. Between 2008 and 2011, for example, Gilead's revenues climbed by about \$1 billion each year, from \$5 to \$8 billion, with their HIV/AIDS medicines making up 85% of that revenue (Gilead Sciences 2012). *Even with this steady rate of growth, however, three historically contingent and institutional factors exposed Gilead to a structural crisis: shareholder-mediated growth as a publicly traded company, patent cliffs on its existing products, and a dry pipeline of potential compounds.* These three factors would each converge to shape Gilead's business model and its position within the innovation process *less as a research and development company but more as an acquisition and regulatory specialist.*

First, as a publicly traded company listed on the NASDAQ stock exchange, Gilead's value to traders and shareholders is determined not by its profits, but by the expectation of *growth* in profits. In other words, value in a speculative market, as discussed earlier and described by Sunder-Rajan (2012), is based on the *potential* for a company's existing or new compounds to generate more in earnings over the present rate of earnings. For companies like Gilead with established flows of revenue, a company is gauged by shareholders on their capability to grow

¹⁴³ Rate of profitability is equal to net income divided by total revenue.

with a particular *magnitude* and *time horizon*.¹⁴⁴ Shareholders typically compare companies' potential for growth against their competitors as well as the cost of capital (or market rate of return). This *differential* rate of accumulation is tied to the notion that owners of capital can allocate that capital to other vehicles for surplus generation. The typical expectation for growth (or 'return on investment') in the pharmaceutical sector is 8-10%, and this growth is assessed by comparing earnings reports against those from previous quarters and the prior year (Damodaran 2017; Rajan 2012).¹⁴⁵ This quarterly and annual time horizon combined with the expected magnitude of growth shapes the evaluations of shareholders as they make bets on given stocks.

Take Gilead in 2011: the company's share price had increased between 2006 and 2008, mirroring its growth in HIV sales. But after this growth began to plateau in 2009 and 2010, its share price slumped, reverting back to its pre-HIV growth era (see Figure 5.6). A piece in *Forbes* magazine at the end of 2010 summed up the sentiment on Wall Street: "As its earlier galloping growth begins to slow, investors are starting to wonder what Gilead plans to do for a second act" (*Forbes* 2010). The fear that Gilead would remain a single disease business, with limited prospects for growth, dictated the company's value rather than its nearly \$8 billion in revenue or high rate of profitability. This focus on share price and expected growth, in turn, was not a natural economic outcome; rather, political-legal shifts have configured the rising power of shareholders over business strategies. This shareholder-driven expectation of growth, however, has influenced and converged with two other institutional and political-economic dynamics to pattern Gilead's position in the innovation process: *looming patent cliffs* and *dry pipelines*.

First, Gilead's existing products had a finite life consequent to the length of their intellectual property protections. Though the threat was not immediate, like those faced by other companies, these expirations – dubbed 'patent cliffs' – still loomed over Gilead's prospects.¹⁴⁶ One of their key HIV compounds, TDF, was set to expire in 2017 in several key markets including

¹⁴⁴ For small companies like Pharmasset with no approved compounds or sources of ongoing profitability, value would be assessed through the progression of its pharmaceutical assets via clinical trials and milestone events, such as initiation of a regulatory approval process. For these smaller companies, trading volume and share price can swing between periods of inertia and quietude to ones of intense volatility and high volumes of trade.

¹⁴⁵ See Damodaran (2017) for cost of capital across US sectors using multiple data sets to arrive at 7.58% for established pharmaceutical companies and 9.25% for smaller biotechnology companies. I discuss the cost of capital further in section 4.3.1.

¹⁴⁶ Many of Gilead's competitors faced the problem of finite patent life even more acutely: by 2012, drugs representing more than \$67 billion in sales were expected to lose patent protection and hence face competition from generic manufacturers (Andersson et al. 2010; Rajan 2012).

Europe, threatening their most lucrative HIV treatment regimens in a little over five years to generic competition (Rangan and Lee 2009). Furthermore, though the HIV treatment regimens were delivering steady revenue growth for Gilead (about \$1 billion each year between 2008 and 2011), they could not deliver the magnitude shareholders demanded over the long-term as the HIV epidemic plateaued (Chandran et al. 2014). Only a new source of revenue could resolve the predicament of the patent cliff and meet those growth conditions. This meant that disease areas like hepatitis C, with existing high priced therapies being used in growing patient populations, presented an important opportunity to generate growth. But generating that growth to replace off-patent medicines within a short-term time horizon was also threatened by another dynamic: dry internal pipelines.

The same shareholder imperative on near-term and continuous growth for a publicly-traded business like Gilead also inhibited the long-term investments required to translate uncertain research into approved therapeutics and new sources of revenue. Rather than investing in long-term research, Gilead distributed capital to shareholders through out the 2000s. Though Gilead's revenue totaled \$33 billion between 2007 and 2011, the company directed \$3.3 billion, or 10%, towards research and development (S&P Capital IQ 2016a). Much of this was allocated to performing late-stage clinical trials on acquired assets in heart disease, as Gilead attempted to diversify beyond HIV (United States Senate, Committee on Finance 2015:667).¹⁴⁷ Meanwhile, the company directed \$9.9 billion to shareholders in the form of buybacks, or 3x their research and development budget.¹⁴⁸

In hepatitis C, the company had advanced two compounds into phase II trials, but both appeared to lack the effectiveness of competing compounds like PSI-7977.¹⁴⁹ Monitoring Gilead's pipeline, Pharmasset's executives noted that "their protease inhibitor is not very potent and has a resistance problem," and observed that their other compound showed the potential for adverse

¹⁴⁷ These acquisitions and clinical trials yielded \$350 million in revenue between 2009 and 2010, as these medicines were for smaller patient populations suffering from specific heart-related problems (Gilead Sciences 2012).

¹⁴⁸ Via the strategies of 'maximizing shareholder value', earnings that could not be used to generate the growth characterized earlier through investments within the firm were expected to be directed to shareholders. I describe these distributions to shareholders – in the form of buybacks and dividends later in this chapter as well as in chapter 5. Gilead directed a bulk of the remainder towards shareholders via share repurchases (or share 'buybacks'), the function and consequences of which we review later in the chapter. See Appendix C for key financial figures for Gilead between 2007-2016.

¹⁴⁹ Interviews 26, 27, 28, 38 provided context into the array of hepatitis C compounds in 2010-2012, and their relative merits and prospects at the time.

heart related events at the necessary dosages (United States Senate, Committee on Finance 2015:667). Unlike Pharmasset's approach to pursue the riskier nucleoside science in developing *sofosbuvir*, Gilead's more modest approach of building on known (and less risky) science via protease and non-nucleoside inhibitors had left its hepatitis C armamentarium empty. Evaluating Gilead's pipeline and looming patent expirations, an analyst with Bloomberg business stated, "We continue to be pessimistic about Gilead's long-term growth", yet noted that he had upgraded the stock from a sell to a buy because of "a large share buy-back plan announced earlier this month" (Jannarone 2011). In this context, long-term investments were eschewed for distributions of capital to shareholders, leaving a shaky pipeline on which to meet the expectations of shareholders.

These twin pressures – patent cliffs on existing treatments as well as the dry pipeline from which to generate new revenue – shaped Gilead's search for near-term growth. To resolve their predicament of generating growth in the context of patent cliffs and limited pipelines, Gilead saw acquisitions as their preferred approach to using their accumulated capital.¹⁵⁰ Reflecting on their position in an earnings call, then CEO John Martin described this strategic preference to Gilead's investors: "We typically like things where we can have impact on Phase III and where we can accelerate those products either into the approval process or into greater indications after the approval process" (Seeking Alpha 2015). In other words, *Gilead's senior leadership saw their company as less oriented around researching and developing new compounds within their own labs, but more as an acquisition specialist delivering near-term growth at the magnitude necessary to meet the expectations of financial markets.*

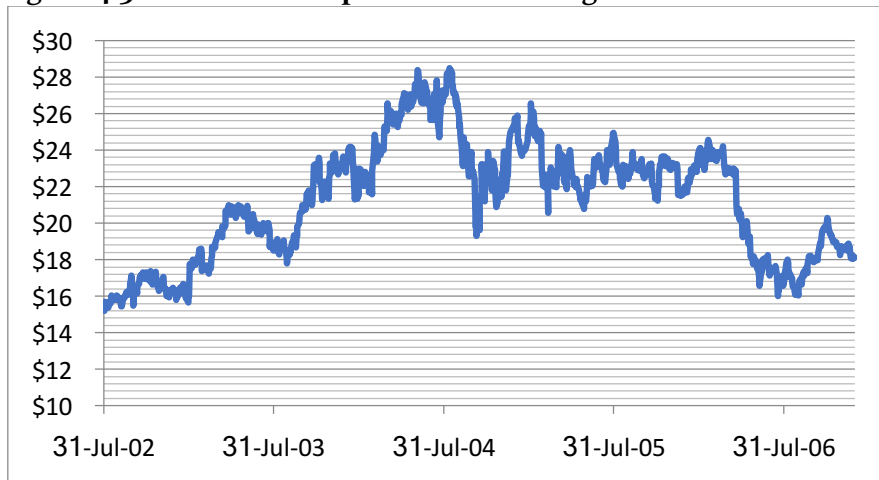
As I introduced in chapter 1 with my description of shareholder control and its role in financialization, Gilead's orientation towards shareholders and financial markets is not a natural phenomenon but part of a historically and politically contingent dynamic (Davis 2009; Lazonick 2015). The shift towards shareholder control began in the 1970 and 1980s with the notion that shareholders in financial markets – and not managers of business organizations, as before – could most efficiently allocate capital across the economy to deliver growth using the metric of share price (Fama and Jensen 1983; Jensen and Meckling 1976). Any investments by a company needed to have the potential to generate growth at the magnitude and within the time horizon described

¹⁵⁰ This approach aligned with and reinforced the seemingly cemented 'performance narrative' pervading the pharmaceutical industry, in which large companies increasingly were to 'outsource' the 'research' side of R&D, leaving it to more nimble early-stage companies and venture capital to perform (Andersson et al. 2010; Gleadle et al. 2014; Montalban and Sakinc 2013).

earlier; any capital that managers believed could not generate this growth, under this view, should be distributed to shareholders (Fama and Jensen 1983; Jensen and Meckling 1976; Jensen 1986). As I describe later in this chapter, regulatory shifts enabling this distribution of capital (through buybacks, primarily) along with linking executive compensation to share price through stock options and awards bolstered shareholder control over the capital allocation strategies of businesses. The extractive logics underpinning shareholder control, which I elaborate further later in this chapter and in chapter 5, created a structural crisis for Gilead.

As 2011 wore on, Gilead knew that losing out on the hepatitis C market could hold potentially dire consequences for the business. Gilead's competitors in hepatitis C, such as Merck and Bristol-Myers Squibb, were long-standing companies with diversified businesses across multiple therapeutic areas (Jannarone 2011). Gilead's reliance on HIV left the business in a vulnerable position, especially if one of its competitors "won" the hepatitis C sweepstakes by coming to the market first or with a best-in-class treatment regimen (Ha et al. 2011). A larger company, for example, could view Gilead's HIV business as an attractive acquisition opportunity, and launch a merger or takeover attempt to gain control over this revenue stream (Jannarone 2011). Transcending its near-term growth crisis would thus be facilitated by a major play in hepatitis C. In August of 2010, Gilead hired John McHutchison, a doctor who led many early-stage clinical trials in hepatitis C for different biotechnology companies - including early stage trials for Pharmasset's PSI-7977 (Gilead Sciences 2010). He had been immersed with the details of the many potential late-stage assets for hepatitis C that were being developed beyond Gilead's labs (Werth 2014). Pharmasset's senior leadership noted the hire, observing "the very clear signals from Gilead and John are that they will be making some strategic moves in HCV" (United States Senate, Committee on Finance 2015:667). We now turn to the intersection of Gilead and Pharmasset's trajectories to unpack the relations of power and dynamics of pricing at stake in financial markets for pharmaceutical assets.

Figure 4.3 Gilead's share price between August 2006 and December 2010



Caption: After rising from \$16 to nearly \$30 on the strength of HIV sales in 2006 thru 2008, Gilead's share value fell and stagnated between \$16 and \$20 in 2010, as sales growth from HIV continued but slowed, and the company did not have another product in the pipeline anticipated to generate new growth. Source: Google Finances, GLD.

4.3 Capitalizing on *sofosbuvir* and the hepatitis C gold rush

In attempting to transcend this structural crisis driven by growth expectations of shareholders, Gilead turned to a pursuit of Pharmasset and its PSI-7977 asset in the summer and fall of 2011. The acquisition process that ensued between Gilead and Pharmasset provides a 'strategic site' for investigating the mechanisms by which the mobilization of speculative capitals behind Pharmasset (and described in section 4.1) converged with the extractive logics driving Gilead's shareholders. Underpinning this acquisition process were valuation dynamics, as both Gilead and Pharmasset determined the right price for a potential transaction by capitalizing the earnings streams each expected to earn from owning PSI-7977. In analyzing capitalization strategies, I go beyond the narrow frame of capitalization as a pricing operation performed by business owners (in this case Pharmasset and Gilead) but, *ala* Veblen, view it as a political-economic vehicle that translated relations of power between multiple actors (state, business, and financial) vying for control over hepatitis C assets (Nitzan and Bichler 2009; Veblen 1908b).

I dissect this capitalization vehicle in three parts, drawing on Pharmasset and Gilead's business plans contained in the US Senate investigation, SEC filings and financial statements,

media accounts, as well as interviews.¹⁵¹ First, I decipher the assumptions embedded in both Gilead's and Pharmasset's valuations of *sofosbuvir* in the summer and fall of 2011 to illustrate the relations of power among multiple actors across the innovation process that in turn shape drug pricing. Gilead's position is revealed not only vis a vis its own shareholders and Pharmasset, but also with a downstream health delivery state. Second, I trace Gilead's position as an 'accumulation center' in the innovation process, by which they converted their accumulated capital from prior sales of HIV medicines into winning *sofosbuvir* in a bidding contest. Finally, I document the 'gold rush' that ensued after Gilead's acquisition to show how the intra-capitalist competition for growth by established pharmaceutical businesses from hepatitis C assets escalated financial speculation in the late stages of drug development.

4.3.1 Project Harry and the relations of power in pricing and valuation

By the summer of 2011, both Pharmasset and Gilead faced a strategic decision over hepatitis C: should they proceed independently or pursue a 'combination'? If they were to undertake a combination with each other, what would be the right price? Each company approached these questions from a different vantage. As I described at the end of section 5.1, Pharmasset plotted the potential for bringing PSI-7977 to patients as a stand-alone company, but recognized the need to scale-up their capabilities in regulatory approval as well as in setting up a global manufacturing and distribution infrastructure. From Pharmasset's vantage, any suitor pursuing an acquisition would need to appropriately value the potential earnings stream that PSI-7977 could bring. Gilead, on the other hand, had few promising avenues other than an acquisition to gain a significant share of the hepatitis C market. To explore this acquisition avenue, Gilead joined with Barclays Capital in 'Project Harry', the internal name given to their joint effort to model the financial value of PSI-7977.¹⁵² The compound, combined with Gilead's long-standing experience in Phase III trials for anti-virals as well existing global manufacturing and distribution channels, could yield the new revenue the company needed to kick-start slumping growth. To make this happen, however, Gilead would need to determine whether and at what price to make such a bet.

¹⁵¹ Interviews 1, 3, 12, 15, 38 contributed insights into the capitalization process.

¹⁵² In Project Harry, Gilead was 'Gryffyndor', Pharmasset was 'Harry', with PSI-7977 the 'golden snitch' – the most potent hepatitis C compound that could serve as the backbone to a curative therapy (United States Senate, Committee on Finance 2015).

As Gilead and Pharmasset weighed these positions and potential strategies, both companies conducted capitalization exercises in order to assess the value of *sofosbuvir* (still named PSI-7977 at the time) to each of their businesses. Described simply by Muniesa (2011:31), capitalization can be conceived of as *the reduction of a stream of future earnings to their present value through the use of a calculative device (a discount rate) which signals how much money a capitalist would be prepared to pay now for a future flow of money*. Gilead would use this calculation to identify how much it would be willing to *pay now* for the future flow of earnings from *sofosbuvir*. Pharmasset, by contrast, would need to determine how much it would need to *receive now* in order give up the potential to accrue earnings from PSI-7977 in the future as a stand-alone company. Rather than understand these exercises in capitalization through the sole lens of a technical device, however, dissecting the assumptions of the calculation reveals the relations of power that are stake in drug pricing and innovation. I focus on two major assumptions here, drawing primarily on data from ‘Project Harry’, Gilead’s joint valuation exercise with Barclays Capital.

The first assumption was the potential price that PSI-7977 could demand upon approval. Gilead, for example, assumed a price of \$65,000 per patient through most of its modeling exercise while also testing a sensitivity range of prices \$10,000 below and above that point (United States Senate, Committee on Finance 2015:792). They chose this figure for *sofosbuvir*’s future price based on the price of the existing standards of care for hepatitis C which was about ~\$50,000 in 2011, and the anticipation that not only would it likely rise by the year of the drug’s approval (estimated to be 2014 in the model), but that buyers would pay more for a superior clinical outcome (United States Senate, Committee on Finance 2015:792). This continued the promise of *pricing escalator* that had mobilized the chain of speculative capital through the innovation process. In making this pricing assumption, Gilead pointed to its anticipation of its relationship with a central actor: the state, and specifically, its public health delivery systems.¹⁵³ Particularly in the US, the largest market for pharmaceuticals, Gilead forecasted their ability to set the price and gain monopoly returns, with a high level certainty about the limited countervailing powers of the state.¹⁵⁴ This relatively open pricing horizon, protected from competition via the patents for PSI-7977, would

¹⁵³ I discuss the dynamics of drug pricing and the ‘health delivery state’ in the following chapter.

¹⁵⁴ Even in other high-income settings (such as Europe and Japan), which would purchase hepatitis C medicines with greater regulatory and negotiating power, Gilead anticipated being able to charge prices in the range of the existing therapies, at a discount to their US launch prices.

shape the valuation that Gilead placed on the compound and the amount they would be willing to bet.

The second assumption was what Muniesa earlier referred to as the ‘calculative device’ – the *discount rate* (Muniesa 2011). The discount rate is used by business managers, in this case the senior leadership teams of both Gilead and Pharmasset, to identify the rate of return (or ‘return on investment’) which must be exceeded to justify an investment. This discount rate is based on a core assumption in financial accounting: a hundred dollars tomorrow is worth *less* than a hundred dollars today. This discount rate is based on a company’s *weighted cost of capital*, which is the rate of return expected by investors and debt holders on the capital it has provided to a business. A failure to generate a return greater than the cost of capital – in this case 10% for Gilead – would mean that an investment is not worth pursuing (United States Senate, Committee on Finance 2015:822).¹⁵⁵

Yet the use of this cost of capital in investment and valuation assessments reveals a crucial relationship of power: between shareholders and business managers. In this configuration, any capital that cannot be used to generate growth greater than the cost of capital would be deemed to be wasteful, and would thus be better directed towards shareholders who could, as argued under the frame of ‘maximizing shareholder value’, more efficiently allocate capital to other firms and sectors in the economy. In this case, the acquisition of PSI-7977 *was* forecast to generate growth greater than the cost of capital (at the price points cited above). However, I follow its role in this capitalization exercise because it reveals how the growth expectations of shareholders structure every capital allocation decision by Gilead’s senior leadership into a simple imperative: either grow greater than the cost of capital within a near-term time horizon, or distribute the capital to shareholders.¹⁵⁶ Though Gilead’s shareholders expected growth to exceed the cost of capital, I later show that shareholders *did not actually risk any capital* into the innovation process behind *sofosbuvir*.¹⁵⁷

¹⁵⁵ See the explainer box for a more detailed primer on these financial accounting methods.

¹⁵⁶ Michael Jensen, one of the leading proponents of ‘maximizing shareholder value’, summed this imperative up when he argued, “The problem is how to motivate managers to disgorge the cash rather than investing it at below the cost of capital or wasting it on organization inefficiencies” (Jensen 1986:23).

¹⁵⁷ In fact, through the mechanisms of share buy backs, Gilead had *reduced* its share count over the prior decade (Seeking Alpha 2015). Yet the high levels of stock-based pay for Gilead’s senior executives tied the strategic interests of shareholders and the managers making these capital allocation decisions. I review both mechanisms later in this chapter, in section 4.4.

Using these two core assumptions, about the future pricing of PSI-7977 as well as the discount rate, Gilead assessed the potential value of a Pharmasset acquisition. Gilead capitalized PSI-7977 through the *net present value* calculation (see Muniesa's earlier definition of capitalization): future cash flows were translated to a present value using a discount rate, with the cost of the possible acquisition then subtracted (United States Senate, Committee on Finance 2015:824). By Gilead's modeling, an acquisition of Pharmasset translated to a net present value for Gilead of \$25.5 billion (after a \$10 billion acquisition price), indicating the vast economic potential of the opportunity (United States Senate, Committee on Finance 2015:810).¹⁵⁸ Furthermore, Gilead believed that it could create greater economic value with PSI-7977 than Pharmasset could alone: though Gilead's internal drug development program had not yielded a backbone compound as promising as PSI-7977, they anticipated that several of their secondary compounds could be used in combination with PSI-7977 to generate a single daily pill regimen that could gain a dominant market position (United States Senate, Committee on Finance 2015:861-862). Paired with their global manufacturing and distribution infrastructure that had previously specialized in anti-viral therapies (with its HIV products), Gilead's modeling encouraged an aggressive posture towards acquiring PSI-7977.

Yet reviewing Gilead's posture reveals the dynamics of a third relationship of power beyond Gilead and its shareholders and Gilead and the health delivery state: its position of power vis a vis Pharmasset and other small companies with pharmaceutical assets. Similar to Gilead, Pharmasset had undertaken its own valuation exercise to assess the value of PSI-7977 if it were to develop it as a standalone company. They arrived at a net present value of \$11 billion, indicating a potentially lucrative economic future for the compound if it were to make it through final Phase III trials (United States Senate, Committee on Finance 2015:888).¹⁵⁹ But Pharmasset forecasted two major barriers to this future as a stand-alone company.

First, unlike Gilead, Pharmasset did not have an existing organizational apparatus for engaging regulatory agencies around the world nor the manufacturing and distribution capabilities required for hepatitis C (United States Senate, Committee on Finance 2015:498-505,

¹⁵⁸ The company's senior leadership placed a high degree of certainty in the compound's effectiveness in Phase III clinical trials, using 100% and 75% as its 'possibility of success' parameters in its sensitivity tests for PSI-7977's value (United States Senate, Committee on Finance 2015:810, 824).

¹⁵⁹ Pharmasset's valuation of PSI-7977 was lower than Gilead's because Pharmasset believed they would need to pair the compound with a secondary compound from another company, thereby splitting the revenue; furthermore, Pharmasset used more conservative assumptions than Gilead based on their lack of existing experience in global regulatory, manufacturing, and distribution capabilities.

507-510). Incumbent firms like Gilead, Merck, and Bristol Myers Squibb already had well-established infrastructure globally; if any of them beat Pharmasset to the market with a hepatitis C treatment (by acquiring another small company with a hepatitis C asset, for example), Pharmasset stood to lose major market share for its lone stream of revenue. Second, Pharmasset, also unlike Gilead with its HIV earnings stream, had no other potential revenue possibilities beyond PSI-7977. Even if it were to build global capabilities in regulatory process, manufacturing, and distribution, Pharmasset would have to quickly diversify to other disease areas and products in order to generate the kind of growth that shareholders would expect (United States Senate, Committee on Finance 2015:501). As I described in the previous chapter, Pharmasset's executives had examined the landscape and deemed that generating such growth from internal research and development would not be possible in the tight frame of 3-5 years, or the time by which growth from hepatitis C revenues was set to plateau and even decline (United States Senate, Committee on Finance 2015:501).

Given these factors, Pharmasset positioned itself for a potential acquisition, realizing that *if an established company like Gilead could value its PSI-7977 compound at the threshold (\$11 billion) that Pharmasset itself did*, then being acquired would be a strategically sound move. The company's shareholders would thereby be assured to make an immediate gain at the level of its anticipated long-term value while forgoing the downstream risks associated with overcoming the barriers to entry I highlighted above. With this determination, Pharmasset's senior leadership aimed to answer the lingering question that they had raised in recent years. Rather than building a durable business, they would instead actualize the very meaning contained in their name: serve a larger pharmaceutical company like Gilead with a promising asset, thereafter making themselves disposable (Berkrot 2011).

In this section, I have provided an extensive account of Gilead and Pharmasset's valuation of PSI-7977 within the context of each of their own businesses, and unpacked a set of relationships of power within which the capitalization process is embedded. First, Gilead anticipated a favorable pricing position with regards to a public health delivery state with limited downstream countervailing power. Second, Gilead's managers had to account for the expectation of growth that its shareholders expected. Finally, through Pharmasset's vantage, Gilead was a better potential suitor than a potential competitor, given Gilead's comparative advantage as an incumbent firm. Taken together, *these factors demonstrate Gilead's position of power within the innovation process to gain control over potential earnings streams via betting on late-stage assets*

and anticipating pricing power with the state – thereby enabling its shareholders to extract value generated through near-term growth.¹⁶⁰ We now turn to whether Gilead would be able to execute on this speculative bet.

Box 4.2 Cost of capital, the discount rate, and net present value: a primer

Cost of capital: *the return expected by those who provide capital for the business*

- Two types of actors may put up capital for a business: investors who purchase equity, and debt holders who buy bonds or issue loans to a company
- Cost of capital and discount rate (see below) are often confused. While related, they are arrived at in different ways and for different purposes.
 - o A company's financial team typically calculates cost of capital; investors use it to assess the risk of a company's equity.
 - o The management team typically takes the cost of capital calculation and then translates that number to a 'discount rate' that must be exceeded to justify an investment.
- The cost of capital is calculated by weighting the cost of a company's debt and equity.
 - o To calculate the cost of debt, take all money the company has borrowed and average the interest rates being paid.
 - o The cost of equity is a more theoretical number, and measures a stock's volatility (a *beta* figure) as well as the market rate of expected return on the stock market (typically 10-12%).
- To arrive at the weighted cost of capital (WACC), take the cost of debt and equity and weight them according to their relative proportions/percentages within the company. For example, if a company has 25% debt at a 4% rate, and 75% debt at a 8 percent rate, the WACC = .25(4%) + .75(8%) = 7%

Discount rate: *the rate that must be exceeded to justify an investment (also 'hurdle rate')*

- Used to calculate the value of future cash flows in terms of present value, based on the idea that money tomorrow is less valuable than money today (*time value of money*).
- Typically set by business managers evaluating a potential investment, using the financial team's cost of capital as a reference point
- Companies will set the discount rate higher than the cost of capital if they are risk-averse and desire a higher rate of return in order to make an investment.

Net present value (NPV): *the present value of an investment's expected cash flows minus the costs of making/acquiring the investment*

- Business managers use this calculation to assess whether an investment should be pursued or made: if the NPV is negative, the project is not a good one, whereas a positive NPV the project might be worth pursuing, with the larger the NPV, the greater the benefit.
- Net present value is calculated using a discount rate (above), which is set based on a business's cost of capital, and management's risk appetite.

*Adapted from Gallo (2014) in Harvard Business Review

¹⁶⁰ I elucidate this extraction in section 4.4, particularly through the distribution of hepatitis C revenues to shareholders via buybacks.

Table 4.5: Key figures used in Gilead and Pharmasset capitalization exercises

	Gilead's Project Harry model (with Barclays Capital)	Pharmasset's Project Knight model (with Morgan Stanley)
Anticipated price for PSI-7977	\$65,000	\$36,000 ¹⁶¹
Cost of capital	10%	8%
Years of sales (from approval year to patent expiry)	2012-2030	2014-2030
NET PRESENT VALUE*	\$25.5 billion	\$11 billion
NPV translated to Pharmasset share price	\$250 per share	\$136 per share
Market price of Pharmasset as of July 2011	\$70 per share, or \$4.8 billion	
Mean target price for Pharmasset forecasted by 16 Wall Street analysts	\$100 per share, or ~\$8 billion	
Final acquisition value	\$137 per share, or \$11.2 billion	

Note: Each of these figures were tested with different assumptions to develop sensitivity ranges, but I am communicating the most relevant numbers here to keep the focus on the core political-economy dynamics.
Source: United States Senate, Committee on Finance, 2015

4.3.2 Betting accumulated capital for acquisition and approval

With these valuation exercises guiding the acquisition process and indicating the positions of power of the multiple actors, Pharmasset and Gilead entered negotiations over a potential acquisition in the late summer of 2011. By early September of 2011, the results of Project Harry and internal deliberations had convinced Gilead's senior management of the value in pursuing an acquisition of Pharmasset for its main PSI-7977 compound (Pharmasset Inc 2011). Over the next twelve weeks, Gilead would navigate between the forecasts of investment analysts, Pharmasset's self-valuation (discussed in the prior section), and competing suitors to ultimately leverage its prior accumulation of capital to gain ownership of the 'golden snitch'.

To make their initial bid, Gilead used the mean and median one-year price targets for Pharmasset forecasted by 16 investment analysts, who predicted a value of \$100 per share (United States Senate, Committee on Finance 2015:811). The market value of Pharmasset was far lower – trading at about \$70 a share in September of 2011 – but these analysts expected that Pharmasset's

¹⁶¹ In their modeling, Pharmasset assumed a price of \$36,000, or about half of what they thought a final regimen would cost (\$72,000). This is because PSI-7977 represented 'half the equation'; though PSI-7977 was the backbone compound, Pharmasset anticipated that it would need to be paired with another compound to be the kind of simple, once-daily treatment with high cure rates that could gain a dominant market position (United States Senate, Committee on Finance 2015:886).

Phase II trial data in late 2011 would boost the share price and increase the value of the company's hepatitis C compound (United States Senate, Committee on Finance 2015). Yet when Gilead bid \$100 per share in September for a total of \$8 billion, Pharmasset's executives rebuffed the offer (Pharmasset, Inc 2011:24-28). Pharmasset's executives had begun reviewing the incoming data from their Phase II trial and privately knew that the positive results would likely surpass the expectations of Wall Street; furthermore, this \$8 billion bid fell below their self-estimated \$11 billion value.

Leveraging this private clinical trial data, Pharmasset drew Gilead into an auction process, inviting multiple companies to review the new evidence confidentially and make bids (Carroll 2011). Sensing the competition, Gilead elevated its acquisition bid now to \$125 per share (Pharmasset, Inc 2011). Yet Pharmasset's executives did not relent; their internal self-valuations of \$11 billion translated to a bid of between \$136-\$146 per share (United States Senate, Committee on Finance 2015:888). The major medical conference held by the American Association for the Study of the Liver (AASLD) would be held in November, and releasing PSI-7977's Phase II trial data at the conference would give Pharmasset a favorable negotiating position (Carroll 2011; Pharmasset, Inc 2011).

Ultimately, the release of this data along with the appearance of competition in the bidding contest motivated Gilead to increase its bid a total of three times (Pharmasset, Inc 2011). On November 20, 2011, Pharmasset agreed to be bought for \$137 per share, for a total value of \$11.2 billion (Pollack and La Merced 2011). This \$11.2 billion figure – the largest ever acquisition of a small biotechnology company at the time – fell right into the range of net present values of the downstream earnings that Pharmasset's senior leadership had anticipated accruing for PSI-7977 as a stand-alone company (Ha et al. 2011; Krauskopf and Basu 2011; Winslow and Loftus 2011). With this bid from Gilead, Pharmasset could guarantee its shareholders this payout *now*, and forgo the multiple downstream barriers associated with bringing a drug to global markets.

Pharmasset's shareholders emerged as big winners from the acquisition, as the \$137 per share value represented a 89% premium from Pharmasset's share price on the last trading day before the announcement (when it traded at \$72 per share). At the time of the acquisition, five institutional shareholders, comprised of pension and hedge funds, held more than 5% of

Pharmasset's shares amounting to an aggregate 39% stake (Pharmasset, Inc 2011).¹⁶² The winners also included the company's executives, which owned 5.3% of the shares, with the CEO Schaefer Price owning 2.4% alone (Thrum 2011). Ray Schinazi, the original founder of Pharmasset, received a \$400 million payment for owning 4.4% of the company (Berkrot 2011; Thrum 2011).

Whether Gilead and its shareholders would 'win' now depended on if the predictions over PSI-7977 would be realized. Within the realm of the financial community, Gilead's bet was perceived as a significant financial risk, with major news stories in the business press each quoting analysts concerned with the size of the acquisition (Ha et al. 2011; Krauskopf and Basu 2011; La Merced 2011; Winslow and Loftus 2011). The Wall Street Journal's 'Heard on the Street' column titled 'Gilead's Risky Revival Procedure' summed up this sentiment (Jannarone 2011):

“With the Pharmasset deal, Gilead has transformed itself into a much riskier company. While all the signs suggest Pharmasset's drug is on a successful path, if something goes wrong, the value of the company could disintegrate.”

In other words, Gilead had traded in financial exposure – by betting a third of the company's market value on a single compound – for reduced technical risk associated with completing a final stage of clinical trials.

Yet in the innovation process, Gilead's shareholders did not risk their capital into the innovation process. Instead, payments from taxpayers provided the bulk of the speculative capital used for Gilead's acquisition. Gilead acquired Pharmasset by leveraging its position as an 'accumulation center' in the innovation process from the prior sales of its HIV medicines to acquire Pharmasset. At the time of the acquisition, Gilead had \$10 billion in cash, accumulated primarily from its sales of Atripla and Truvada (Gilead Sciences 2012; S&P Capital IQ 2011b; 2012).¹⁶³ These sales were in part driven by price increases, with Atripla, for example, rising from \$13,800 per year in 2006 to \$25,874 per year by 2011 (Fair Pricing Coalition 2015; Rode 2011). Payment for these treatment regimens came from public sector programs across high-income countries. Even in the US with large private insurance markets, the public sector finances

¹⁶² From Pharmasset's acquisition SEC filing, these five institutional shareholders with more than 5% in share ownership were: Fidelity Management (12.6%), Capital World Investors (10%), T. Rowe Price (5.6%), Capital Research Global Investors (5.6%) and Baker Brothers Advisors (5.4%).

¹⁶³ As a reminder, both Atripla and Truvada are based on two compounds *TDF* and *emtricitabine* which were both licensed. *Emtricitabine* can be traced to Triangle Pharmaceuticals, which was also started by Ray Schinazi and based at Emory University, where Schinazi drew on NIH funding to sustain his early research into the drug (Cohen 2015).

treatment for over 50% of all individuals diagnosed with HIV through a special government program begun with the AIDS epidemic in the mid-1990s, and 80% of all HIV patients in the US are on a Gilead treatment regimen (Petersen 2016b; Pund, Lefert, and Bowes 2016).

To come up with the \$11.2 billion required, Gilead spent \$5.2 billion of this HIV cash, saving the rest to pay down previous debt or finance future acquisitions and share repurchases (Gilead Sciences 2012; S&P Capital IQ 2011b; 2012). Gilead also leveraged this accumulated capital to raise new debt, which it used to pay for the remaining \$5.9 billion of the acquisition (Gilead Sciences 2012; S&P Capital IQ 2011b; 2012). Gilead's betting capital, then, hinged on the prices paid for its prior HIV drugs, much of this financed by public sector programs. Gilead's shareholders, on the other hand, had not risked any capital into the innovation process; instead, they continued to trade Gilead's shares on the anticipation of *sofosbuvir*'s Phase III clinical trials.

With the backbone *sofosbuvir* compound now in hand, Gilead fashioned a clinical trial strategy bearing the imprints of its HIV approach: bringing multiple compounds together to create a single daily oral pill (see Table 4.7 for a summary of Gilead's clinical trial strategy). Gilead, like many established companies, had experienced recent success in developing compounds for the NS3/4 protease and NS5a polymerase targets; yet each of these compounds was useless on their own as they did not attack the pivotal NS5b polymerase (Link et al. 2014; Pawlotsky 2013).¹⁶⁴ With *sofosbuvir*, Gilead now completed the hardest part of the puzzle by finding the backbone compound necessary for a simplified treatment regimen. The company's scientists and management team thus envisioned a "combination strategy", in which Gilead would bring together *sofosbuvir* with its internal secondary compounds in a series ("waves") of phase III trials (United States Senate, Committee on Finance 2015). Each of these trials confirmed Gilead's confidence in the PSI-7977 compound, with the trials indicating near 100% cure rates (Afdhal et al. 2014; Jacobson et al. 2013; Lawitz et al. 2013). The FDA designated *sofosbuvir* a 'breakthrough therapy', enabling Gilead to pursue an expedited approval process and move their anticipated launch date forward by almost a year (Sherman et al. 2013; United States Senate, Committee on Finance 2015).

¹⁶⁴ Gilead provided the clinical trial costs below for these secondary compounds used in combination with *sofosbuvir*. However, I did not document their discovery as these internally developed compounds did not offer a major therapeutic advance on their own and were in the same class as compounds developed by many other labs. Their only value came in combination with *sofosbuvir*, which was the sought-after backbone compound.

Taken together, Gilead reported spending \$880.4 million on clinical trials for *sofosbuvir* and its combination therapies (United States Senate, Committee on Finance 2015:23), allowing us to account for the costs of development for *sofosbuvir*-based medicines across Pharmasset and Gilead (see Table 4.6 below).¹⁶⁵ Like with Gilead's \$11 billion acquisition, it was the accumulated capital from prior sales, not the capital of its shareholders, that enabled Gilead to complete these clinical trials. On December 1, 2013, two years after Gilead's acquisition of *sofosbuvir*, the FDA approved the treatment (Pollack 2013), with the company setting its launch price north of \$80,000 – a decision I dissect in chapter 5.

As described later in this chapter, Gilead's shareholders would make major gains as the compound went to market in late 2013. Before unpacking the Gilead's capital allocation decisions with their newfound hepatitis C revenues, however, I illustrate that the political-economic dynamics that shaped the trajectory of *sofosbuvir* were not unique or exceptional in the realm of hepatitis C drug development. A comparison with other hepatitis C assets and Gilead's competitors reveals a pattern of speculation and shareholder control, in which a struggle for growth between businesses escalated the speculative costs of the innovation process in its final stages.

Table 4.6 Main *sofosbuvir*-related clinical trial costs by Pharmasset and Gilead

Trial sponsor	Phase	Reported cost for <i>sofosbuvir</i> specifically	All R&D costs during period of <i>sofosbuvir</i> development
Pharmasset	Pre-clinical to Phase II trials	\$62.4 million	\$281 million (2001-2011)
Gilead	Phase III combinations (actual)	\$880.3 million	\$4.02 billion (2012 – 2013)
	TOTALS	<i>Sofosbuvir-based regimens = \$942.5 million</i> <i>Estimated costs of sofosbuvir alone (based on Pharmasset estimate – see below) = \$62.4 + \$90.5 million = \$152.9 million</i>	Total costs of all R&D: \$4.3 billion

Source: US Senate Finance Committee (2015:23-24)

¹⁶⁵ I return to an interpretation of these costs after a review of Gilead's pricing strategy and revenues from hepatitis C. For now, I note that the costs of *sofosbuvir*'s development was \$942.5 million, with the costs of *all* R&D across Pharmasset and Gilead during the time of its development was \$4.3 billion.

Table 4.7: Gilead's combinations of *sofosbuvir* as part of their 'wave' strategy

Wave	Compounds / Targets	Brand name	Approval/launch date
Wave 1	Sofosbuvir* + ribavarin (and inteferon in certain sub-groups)	Sovaldi	December 2013
Wave 2:	Sofosbuvir + Ledipasvir (NS5a inhibitor)	Harvoni	October 2014
Wave 3	Sofosbuvir + Veltapasvir (NS5a inhibitor)	Epclusa	June 2016
Wave 4:	Sofosbuvir + Veltapasvir + Voxilaprevir (NS3/4a protease inhibitor)	N/A (not approved yet)	Application submitted by Gilead, December 2016

*Sofosbuvir is NS5b inhibitor

4.3.3 A speculative gold rush and the struggle for hepatitis C assets

The dynamics of speculative capital and shareholder control that governed *sofosbuvir*'s journey would also influence the directions of other compounds for hepatitis C. In fact, Gilead's acquisition intensified these dynamics, leading to a 'hepatitis C gold rush' (Swann 2013). Soon after the \$11.2 billion acquisition, investment analysts predicted more such speculative activity. "These deals tend to happen in waves," said Dan Veru, who had managed an investment fund with Pharmasset shares (Tirrell and Lachapelle 2011). The reason: Gilead's competitors still held out hope to catch the 'golden snitch' (in case *sofosbuvir* unexpectedly failed in Phase III trials), or at the very least gain a share of a market with escalating value.¹⁶⁶ Andrew Berens, an analyst with Bloomberg, predicted, "We are going to see a *land grab* to try and get companies that are developing them" (Tirrell and Lachapelle 2011). His prediction came to fruition, with large companies making a play for a series of late-stage assets in the months and years following Gilead's purchase. These deals reflect two of the key features that shaped the innovation process behind *sofosbuvir*: the speculative features of markets for pharmaceutical assets as well as the shareholder-driven strategies of large, established pharmaceutical companies (see Table 4.8).

First, Gilead's large valuation of *sofosbuvir* escalated the price of other hepatitis C assets that had entered their later stage clinical trials even with therapeutic outcomes less potent than those realized by *sofosbuvir*. For example, within a month of Gilead's acquisition, Bristol-Myers Squibb announced that it had bought Inhibitex for its INX-89 asset at a price of \$2.5 billion, or \$26 dollars per share (La Merced 2012). On the prior day of trading, the company had been valued at \$9 per share, with its shares hovering even lower at the time of Pharmasset's acquisition (La Merced 2012). Two years later in June 2014, Merck made a similar move, buying Idenix for its IDX-

¹⁶⁶ Ultimately *sofosbuvir* would be the best compound and gain almost the entire market 'share' for hepatitis C (nearly 90%), with other companies and assets gaining only a small slice.

21437 asset at a price of \$3.85 billion, translating to \$24.50 per share (Pollack 2014). On its previous day of trading, Idenix had been valued at \$7 per share (Pollack 2014). The potentially lucrative market in hepatitis C, underscored by Gilead's bet on *sofosbuvir*, drove the valuations of these smaller companies.

Second, these large companies operated similarly to Gilead in the hepatitis C innovation process: as acquisition specialists aiming to generate new growth through owning a hepatitis C asset. BMS, for example, anticipated losing their best-selling Plavix to generic competition in May of 2012, leaving the company without an asset that had generated 1/3 of the company's revenue in 2011 (Staton 2012; Team 2013). Inhibitex's INX-89 offered a potential route to compete with Gilead and replenish lost revenue. Merck, too, had long viewed hepatitis C as a vehicle to deal with an impending patent cliff facing three of its best-selling medicines – Remicade, Cubicin, and Zetia – in 2017 (Campbell 2016). This left the company vulnerable to losing \$4 billion in revenue to generic competition (Campbell 2016). With Gilead racing ahead with *sofosbuvir*, Merck aimed to enter the hepatitis C market via the acquisition and gain a piece of the market share (Pollack 2014). Each of these companies, dominated by the expectations of shareholders detailed earlier in this chapter, aimed at acquisitions in the late-stages of the innovation process to generate growth in the face of dry pipelines and patent cliffs.

These acquisitions echo Veblen's view of assets in the economy, with an intra-capitalist struggle over future earnings streams leading to an escalation of speculative bets in the late-stages of the innovation process (Birch 2016; Veblen 1908a). The costs of these acquisitions were not tied to the size of investments in the tangible dimensions of drug development, but rather fastened to the demand logics of assets in financial markets: the prices for these assets rose in parallel to their demand, as companies sought to gain control over potential revenue growth.

Table 4.8 Major transactions in hepatitis C between 2011 – 2015

Acquired Company	Acquiring Company	Value and Timing of the Deal	HCV asset of interest	Current status
Pharmasset	Gilead Sciences	\$11.2 billion, 11/2011	PSI-7977	\$45 billion in revenue for Gilead
Inhibitex	Bristol Myers Squibb	\$2.5 billion, 1/2012	INX-89	Abandoned in Phase III trials after patient death
Idenix	Merck	\$3.85 billion, 6/2014	IDX-21437	Competing with Gilead for 10% market share
Achillion	Johnson and Johnson (Jansen)	\$1.1 billion, 5/2015*	ACH-3102	In Phase III trials, aiming to come to market in 2018

*value of partnership deal, rather than outright acquisition

Sources: Pollack (2013), De La Merced (2012), Tirrell (2011), and Loftus (2014).

4.4 Buying back or paying forward? Following Gilead's hepatitis C revenues

Amidst these companies racing for hepatitis C revenues, Gilead gained approval for their hepatitis C medicines first, in December 2013, and rapidly accumulated capital from their sales. While Gilead's pricing strategy for these medicines is the subject of the following chapter in which I document the deployment phase of the innovation process, in this section I use Gilead's financial reports to detail the company's position as an accumulation center to perform its other function in the innovation process (besides bet on late-stage acquisitions): distribute capital to shareholders. Tracing the flow and uses of this capital further illuminates the extractive processes driven by Gilead's shareholders (and the ways in which they exert control over business executives and corporate strategy) which I introduced earlier in this chapter.

Between their launch in December of 2013 until the end of 2016, Gilead accumulated \$46.4 billion in worldwide revenue from *sofosbuvir*-based regimens. In the space of three years, Gilead's total revenues as a business tripled, from \$11.2 billion in 2013 to \$32.6 billion in 2015 (Gilead Sciences 2017). Hepatitis C sales drove this escalation in revenue, accounting for 60% of all sales in 2015 and 50% in 2016, with the remainder coming largely from their steadily growing HIV sales (Gilead Sciences 2017). With the relatively low cost of production for its HIV and hepatitis C medicines, the company's gross profits were 87% of their revenues, totaling to \$76.3 billion between 2014 and 2016 (Gilead Sciences 2017).¹⁶⁷ The company's executives had significant capital allocation decisions to make with their newfound hepatitis C sales.

4.4.1 The cannibalized company and Gilead's share buybacks

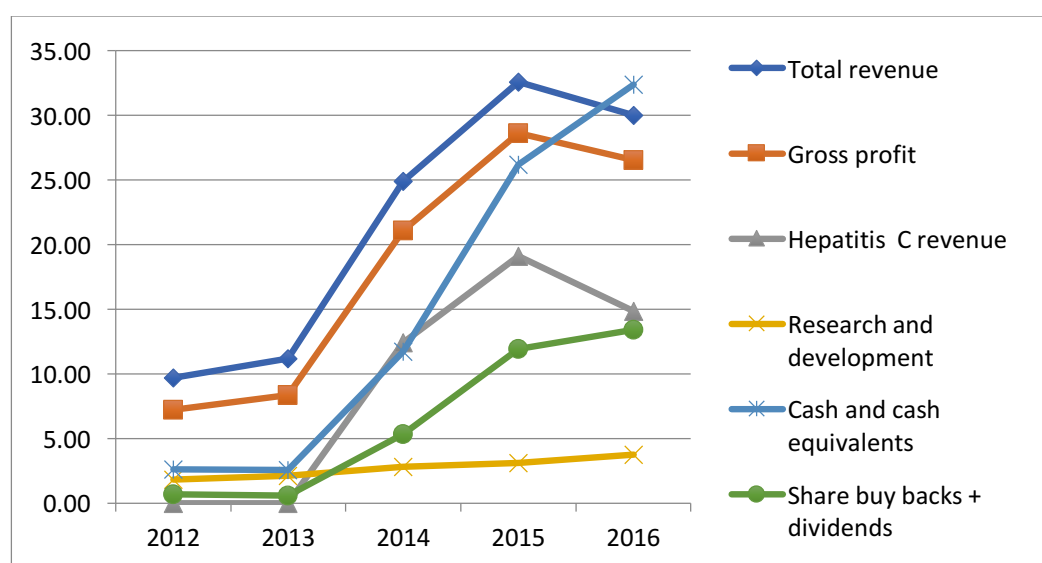
Where did these earnings go? Of this \$76.3 billion in gross profits, Gilead's executives stockpiled \$32.4 billion in cash and cash equivalents (short-term debt) by the end of 2016 (after ending 2013 with \$2.6 billion in cash) for potential acquisitions and distributions of capital to shareholders (Gilead Sciences 2017). Additionally, the company directed \$30.7 towards share buybacks and dividends in those years (Gilead Sciences 2017).¹⁶⁸ In other words, Gilead's leadership translated 79% of its gross profits over three years into a cash stockpile and

¹⁶⁷ Gross profit is total revenues minus the cost of goods sold (the manufacturing and production costs of Gilead's medicines). I cite this figure here as it presents the total sum with which Gilead's senior leadership then made capital allocation decisions.

¹⁶⁸ Of this total, \$4.36 billion were dividends and the \$26.3 billion were buybacks. Gilead only began to offer dividends in the second quarter of 2015.

distributions of capital aimed at shareholders.¹⁶⁹ By contrast, the company reported spending \$9.67 billion, or 12.6% of their gross profits in this period, towards research and development (Gilead Sciences 2017).¹⁷⁰ Figure 4.7 depicts Gilead's revenues and gross profits, as well as their capital allocation strategies.¹⁷¹ Though I return to the dynamics around Gilead's stockpiled cash in chapter 5, here I focus on the level of distribution to shareholders because they demonstrate a recurring theme from this chapter: the extractive relationship between Gilead's shareholders and the innovation process.

Figure 4.4 Gilead's revenues and capital allocation decisions, 2012-2016 (in billions)



Source: Gilead's SEC Filings

Of the \$30.7 billion that Gilead's executives distributed to shareholders, \$26.3 billion were for share buybacks (or 'repurchases'), with \$4.36 billion in dividends (Gilead Sciences 2017). By buying back their own shares, Gilead's executives aimed to raise the value of the remaining ones (Ezekoye, Koller, and Mittal 2016) and promote near-term *trading* with the aim of boosting the

¹⁶⁹ This 79% figure represents \$29.8 billion in additional cash with \$30.7 billion in buybacks and dividends (for a total of \$60.5 billion) divided by \$76.3 billion in gross profits. For context: the annual budget for the entire US National Institutes of Health has hovered at the \$30 billion level in recent years (NIH 2017a).

¹⁷⁰ Though Gilead did not provide a break-down of their research and development expenses, they noted in their SEC filing that a significant bulk of their expenses was aimed at clinical trials; from the Senate investigation as well as other filings, we can surmise a major share of this cost to be their late-stage trials for *sofosbuvir* combinations as well as a new HIV compound aimed at extending their patent protection, which I describe further in chapter 5.

¹⁷¹ General operating expenses as well as taxes account for the remaining use of the gross profits.

share price.¹⁷² Such buybacks, however, illustrate the ways in which the growth logics fueling shareholders (described in section 4.2) ultimately drive extractive processes. In this configuration, the generation of growth at the magnitude and within the time horizons expected by shareholders meant that Gilead's senior leadership only reinvested a small fraction of the company's earnings back into research and development, with those reinvestments positioned primarily to fund the late stage clinical trials that could lead to the kind of near-term growth demanded in financial markets (Gilead Sciences 2017).

Signaling the perceived absence of other directions for investment, Gilead's senior leadership used buybacks as a way to 'maximize shareholder value', with shareholders deemed in this configuration to be the sole residual claimants on Gilead's 'free cash flow' – as the only economic actors argued to risk capital without a guaranteed market rate of return (such as via wages or contracts) and as 'efficient allocators' of capital across the economy. Though these arguments are the prevailing wisdom in corporate governance, they are in tension with the facts of the *sofosbuvir* innovation process.

As I have showed with *sofosbuvir*, Gilead's shareholders did not risk any capital into the innovation process – they traded on the company's stock price. Lazonick has shown how buybacks only aimed to boost this trading, and thereby Gilead's share price – not drive investment, such as further biomedical innovation in areas of unmet medical need (Lazonick et al. 2016). Though dividends are thought to encourage share *ownership* by providing a quarterly reward on a per-share basis, buybacks are observed to have the opposite effect by promoting *trading* on the anticipation of changes in share price (Ezekoye et al. 2016; Lazonick et al. 2016). In this way, shareholder control both limits reinvestments in long-term research efforts within the firm and drives the distribution of earnings towards shareholders to propel speculative stock trading. A Reuters investigation into the rise of buybacks across large publicly-traded U.S. businesses provided an apt name for this strategy: the 'cannibalized company' (Brettell, Gaffen, and Rohde 2015).¹⁷³

¹⁷² One way this happens is by artificially boosting the *earnings per share (EPS)* ratio, a key financial indicator used by traders to buy and sell stocks: reducing the share count reduces the denominator (*earnings/shares*), making the stock potentially more attractive to traders in the near-term (Ezekoye et al. 2016).

¹⁷³ This approach reproduced the structural crisis that I described earlier, and which I discuss further in chapter 5.

Yet share buybacks are not a natural feature of corporate strategy and financial markets. Rather, they are a function of particular historical and institutional changes, of which I detail two: 1) regulatory shifts by the U.S. state that have enabled this distribution of capital to shareholders through buybacks and 2) the power relations that shareholders assume over senior executives through stock-based compensation. Before the 1980s, companies purchasing their own shares at such high levels would have been deemed to be engaging in illegal and manipulative stock trading. On November 17, 1982, however, the U.S. Securities and Exchange Commission promulgated Rule 10-b-18, which gave companies ‘safe harbor’ against charges of manipulation in pursuing such transactions (Lazonick 2015). This rule change gave companies another strategy to direct earnings to shareholders beyond the use of dividends. In the subsequent decades, share buybacks have grown as a corporate practice, with data from the prior decade indicating the scale of its effects. For example, the 19 pharmaceutical companies on the S&P 500 Index expended a total of \$226 billion on buybacks during the years of 2005 to 2014, equivalent to 51% of their combined R&D expenditures (Lazonick 2015).

This SEC rule change came as part of the Reagan administration’s de-regulatory agenda, with a former brokerage executive, John Shad, heading the SEC at the time. Shad described his agenda in a New York Times piece: “To facilitate the accumulation of capital by corporations by removing regulations” (Gerth 1981). But as I have illustrated with Gilead, the SEC rule change would have a much more paradoxical effect: though corporations could accumulate more capital, this capital did not stick around within the corporation (Lazonick 2015). The buyback rule facilitated the *distribution* of this capital to purchases of a company’s own shares. The use of this buyback strategy to distribute capital to shareholders relied on a second dynamic beyond the SEC rule-change: linking the strategic interests of senior executives with those of shareholders.

4.4.2 Structuring executives to disinvest and distribute capital

Institutional shareholders during the 1980s and 1990s increasingly looked to tighten the tie between the interests of shareholders and senior executives by pushing corporate boards to significantly increase the proportion of executive compensation coming from stock options and awards (Lazonick 2015). The rise in executive pay over the last three decades – with senior executives today earning 949:1 of the average worker – has been attributed to this shift towards

offering stock-based compensation (Lazonick and Hopkins 2016).¹⁷⁴ In this permissive regulatory environment, I focus less on the actual rise in executive compensation, but the capital allocation strategies that shifts in compensation have incentivized.

Gilead's senior executives fit what is now a common pattern, with their compensation also coming largely from stock-based pay (Gilead Sciences 2016b). Between the years 2014-2016, for example, Gilead's top five executives made a total of \$1.07 billion in compensation (see Table 4.9). Of this sum, 95% came in the form of stock options and awards in the years 2014 and 2015, and 80% in 2016 (Gilead Sciences 2016b). As Gilead's shares rose on the strength of hepatitis C sales and as their executives directed \$26.3 billion towards share buybacks, they also exercised their options and grant awards to make sizeable gains on the upside of Gilead's ascending share price. As shareholders themselves, Gilead's senior executives has been structurally incentivized to distribute capital to shareholders and stockpile cash for potential acquisitions, rather than reinvest in long-term projects.¹⁷⁵

Table 4.9 Compensation for Gilead's Top Five Executives, 2014-2016

(All figures in Millions)	2014	2015	2016*	
John Martin(CEO, now retired)	\$192.80	\$231.96	\$98.15	
John Milligan (COO, now CEO)	\$89.50	\$103.35	\$58.10	
Gregg H. Alton (EVP)	\$56.20	\$22.57	\$8.50	
Norbert Bischofberger (Head of R&D)	\$50.70	\$95.53	\$7.00	
Robin L. Washington (CFO)	\$26.60	\$21.97	\$5.53	
<i>Percent from stock-based pay</i>	95%	95%	80%	
TOTAL COMPENSATION	\$415.80	\$475.37	\$177.28	\$1,068.45

Source: Gilead's SEC 14-A Proxy filings, 2014-2016

*We discuss the reason behind the 2016 decline in executive pay and share-based compensation in the following chapter.

¹⁷⁴ Legislation from the U.S. Congress aimed at addressing the rise in executive compensation – principally through the Dodd-Frank bill after the financial crisis – has to date shown little effect as key provisions have yet to be enacted, such as the disclosure of pay ratios between executives and workers. I do not review the full array of legislation that has sought to regulate executive compensation patterns over prior decades, but focus more narrowly on the link between stock-based compensation and the buyback strategy it incentivizes.

¹⁷⁵ By 2016, this buyback strategy began to falter in the aim of rising Gilead's share prices, however, for reasons I discuss in chapter 5 and which are also intimately linked to the speculative and shareholder-dominated features of the innovation process.

4.4.3 An offshore tax haven for *sofosbuvir*

Thus far, I have illustrated buybacks and cash stockpiles to be the major destinations of Gilead's accumulated capital, rather than research and development within the company. Another potential destination – paying taxes to the US state, which had made critical contributions to the innovation process – was diminished through Gilead's maneuvers of their intellectual property protections over *sofosbuvir*.

In a February 2013 earnings call, Robin Washington, Gilead's Chief Financial Officer counseled investment analysts: "the IP (intellectual property) of 7977 (*sofosbuvir*) is domiciled in Ireland, so as we commercialize that, there is opportunity for our tax rate to decline over time" (S&P Capital IQ 2013). In other words, Gilead had transferred the ownership claims over its *sofosbuvir* property to one of its 6 Irish subsidiaries, and created a licensing arrangement through which it reported lower US profits (Rice and Clemente 2016). The outcomes of this strategy are reflected in several key financial metrics. First, while two-thirds of Gilead's hepatitis C sales are in the US, they report only 37% of their profits domestically and assign the rest to places with lower or no taxes, making for a 1% foreign tax rate (Gilead Sciences 2017). Second, Gilead's accumulated offshore profits mirror their surging hepatitis C revenue, rising from \$8.6 billion in 2013 to \$28.5 billion in 2015 (Gilead Sciences 2017). Third, Gilead's US tax rate fell by 40%, from 27.3% in 2013 to 16.4% in 2015 (Rice and Clemente 2016). Such metrics culminate in a significant magnitude of tax avoidance: a report released by the Americans for Tax Fairness found that Gilead had avoided \$10 billion in US taxes by 'domiciling' *sofosbuvir* in Ireland (Rice and Clemente 2016).

Gilead's strategy is enabled by 'legal loopholes' in the US tax code, by which companies routinely avoid paying the 35% corporate tax rate by holding earnings overseas (Rubin 2015). Companies have argued that the US tax rate is non-competitive for making domestic investments, making these 'tax planning' maneuvers to be a matter of survival (Rubin 2015). Yet when Congress and the Bush administration temporarily lowered the tax rate on profits to be repatriated from 35% to 5.25% in 2005, companies did not direct this capital towards investment (Kocieniewski 2016). Of the \$300 billion in repatriated profits from 800 companies, 92% of the money was used for the type of share buybacks and executive bonuses described in this section (Kocieniewski 2016). These loopholes and distributions of capital can be juxtaposed against the ongoing threats to the US NIH budget, whose investments were critical to the *sofosbuvir* innovation process.

In following the flow of capital from *sofosbuvir*-based medicines in section 4.4, I have illustrated the extractive processes shaping Gilead's business strategy as manifested in share buybacks, sizeable stock-based executive compensation, and tax avoidance.

4.5 Taking stock of speculative capital and shareholders: a summary

Over the course of four parts, this chapter demonstrated the processes constituting the financialization of *sofosbuvir*. Pharmasset's control over intangible hepatitis C assets mobilized speculative capitals from a chain of financial actors on the anticipation of rising prices (the pricing escalator) and market valuations and the opportunity for capital gains on the entry and exit of ownership stakes in the company. Without any approved products and sales nor the investments to develop the organizational capabilities for a durable business, Pharmasset viewed large companies like Gilead better as potential suitors than future competitors – with an acquisition offering the chance to gain a major reward for Pharmasset's shareholders while passing off the technical risks for end-stage drug development to the acquiring company.

In this context, Gilead – and other large, publicly traded pharmaceutical companies – faced a structural crisis due to the continual and near-term expectations of growth driving Gilead's shareholders. To overcome this crisis, Gilead pursued an acquisition of Pharmasset, betting its accumulated capital from prior HIV sales (and using it to leverage debt) on the *sofosbuvir* (PSI-7977) compound. Gilead's position in the innovation process as more an acquisition specialist than a research and development organization illustrated the extractive logics driving the company's shareholders. Gilead's \$11.2 billion bet – part of a speculative gold rush in the late stages of hepatitis C drug development – was based on Gilead's anticipation of charging the health systems higher prices in the future than the existing standard of care in exchange for therapeutic improvements. Though Gilead's shareholders had not risked any of their own capital into the innovation process, their control over capital allocation decisions (i.e. through linking executive compensation to share price) led the company's senior leadership to distribute a bulk of Gilead's hepatitis C earnings to shareholders. Along this process, the state provided the knowledge assets that activated the curative value of *sofosbuvir* with the McGuigan method, but also governed the rules by which capital mobilized in its different forms, from the emergence of venture capital to the escalation in share buybacks.

The financialization of drug development is marked by a distribution of risks and rewards across the innovation process which I review more fully in chapter 6. But some preliminary

observations are possible. In this chapter, I demonstrated that the owners of speculative capital in the earlier stages of drug development were motivated by compressed cycles of risk-reward, in which they attempted to gain a reward based on their ability to enter and exit ownership in time periods far shorter than the lengthy period of drug development. As for Gilead's shareholders, they did not risk capital into the innovation process, as the company converted its accumulated capital from patent protected prices of its HIV medicines into the speculative capital necessary to acquire *sofosbuvir's* potential earnings stream from Pharmasset. Yet Gilead directed its accumulated capital from hepatitis C towards maximizing shareholder value and future acquisitions while also using loopholes to avoid taxes to the US state, which had risked its patient capital to shape the direction of the innovation process. Finally, the pricing and valuation strategies underpinning these speculative and extractive processes would ultimately impact patient and public health outcomes. We now turn to an analysis of the deployment phase of the innovation process to better understand these specific impacts and the dynamics that produced them.

Chapter 5. Waiting on Value: Gilead's Pricing and the Crises of the Triage State and the Patient Cliff

"It is crystal clear to me that the body is an accumulation strategy in the deepest sense"

- Donna Haraway (1996: 510)

As Gilead launched their *sofosbuvir*-based regimens 2013 and 2014, the hopes of millions of patients with hepatitis C appeared fulfilled: the toxic, interferon-based regimens would now be cast aside, opening the way to near 100% cure rates with a shorter treatment that triggered few side effects (Hagan and Schinazi 2013; Pollack 2013; Rice and Saeed 2014). Along with its clinical marvels, the medicine also appeared poised to be a financial marvel for Gilead, with large patient populations and high potential launch pricing leading to significant revenue growth (S&P Capital IQ 2013). Yet these hopes were short-lived, and by 2016, both patients and Gilead viewed these medicines in a diminishing light, with deferred treatment access and waning financial success (Crow 2016a; Hoofnagle and Sherker 2014; Nisen 2017; Ward and Mermin 2015). This chapter illustrates these confounding outcomes in the deployment phase¹⁷⁶ of the innovation process, tracing the relationships between Gilead, public health delivery systems, and financial markets.

In understanding these outcomes, this chapter traces forward the influence of financialization introduced in the prior chapter, with speculative and extractive dynamics shaping Gilead's launch prices for *sofosbuvir*, the deployment of the medicine, as well as the reproduction of financialization for future innovation processes. Gilead's pricing strategy culminated the pricing escalator observed with the mobilization of speculative capitals, in which the company priced *sofosbuvir* using the reference price of the existing standard of care as a floor and estimated the upward limits of what health systems would be willing to pay for improved therapeutic outcomes. This pricing strategy created a crisis of treatment access, budgetary stewardship, and public health planning for the state: the health delivery state turned into a triage state and

¹⁷⁶ The dynamics unfolding in this stage are important in two respects. First, the adoption and use of an innovation is, by most common definitions, intrinsic to the innovation process itself. See chapter 2 (section 2.1.2) for more on my definition of the innovation process, and the inclusion the deployment phase. In this stage, the extent and types of rewards accrued through an innovation are no longer a matter of anticipation: they can be directly observed. For example, we can account for the rewards in a more comprehensive manner by following the extent to which *sofosbuvir* benefited patients and public health as well as influenced Gilead's business strategy. A second reason for studying this stage: the evidence from the deployment stage of innovation can give us clues to the reproduction and sustainability of the innovation processes for the future.

exercised limited countervailing power vis a vis Gilead and the ‘value-based’ logics of drug pricing at play. Finally, a curative therapy revealed the dynamics *reproducing* financialization and their stark consequences for future innovation: even with rates of profitability exceeding 40% in 2015 and 2016, Gilead’s inability to meet financial market expectations of continuous growth with a curative therapy reinforced the company’s extractive and speculative strategies in ways that promoted distribution of revenues to shareholders, the accumulation of capital for acquisitions, and a focus on incremental therapeutic advances for a ‘chronic market’ rather than more radical innovation (Chen 2017). I trace the mechanisms that constitute this deployment phase of the innovation process in three parts.

First, I chronicle Gilead’s approach to pricing their regimens in section 5.1 to show the rationale they used and situate it in the wider context of the *pricing escalator* that had mobilized the speculative capitals presented in the prior chapter. This account is based on a close analysis of the US Senate investigation and the associated appendices of Gilead’s internal corporate documents along with interviews and observation at meetings.

Second, I trace the consequences for Gilead’s pricing on health systems and patients in section 5.2 to evaluate the extent of health outcomes experienced by patients and public health systems, drawing on public policy reports, media accounts, multiple interviews, and observations at meetings. Furthermore, I map the relations of power between the state and drug manufacturers vis a vis drug pricing and the logics of value at stake.

Finally, section 5.3 documents how the mechanisms underpinning financialization produced another episode of crisis for Gilead and in turn shifted the company’s business strategy towards prioritizing short-term growth. The company pursued a major marketing campaign to increase hepatitis C uptake, a financial cycle of acquisitions and buybacks, and increased attention on ‘innovation’ for *chronic over curative* therapies.¹⁷⁷ An examination of each of Gilead’s earnings call transcripts over a two-year span (2014-2016), transcripts from investor meetings, and media accounts shaped the interpretation of this stage of the process.

What emerges across these three parts is a narrative of ‘waiting on value’, in which the financial dynamics of a curative therapy in the hands of Gilead sustains a dual crisis: patients waiting for the health value of a cure and shareholders waiting for the value of near-term and

¹⁷⁷ By chronic versus curative, I mean therapies that require patients to take a treatment over a life-time (“chronic”) versus therapies that can end a disease process to the point where medicines are no longer required (“curative”). I explore this in the context of HIV, which currently is a disease for which patients must take life-time treatment.

continuous growth that a curative therapy cannot durably deliver. Upon this final stage of accounting, I will take full stock of the innovation process in chapter 6.

5.1 Setting a price for a cure: Gilead's \$1,000 a day pill

On December 2, 2015, the US Senate investigation offered a rare opportunity: an inside-look at the black box of pharmaceutical pricing from within a business (Loftus 2015; United States Senate, Committee on Finance 2015).¹⁷⁸ Lifting this black box is crucial for three reasons. First, it enables an understanding of the proximate factors that shaped Gilead's *sofosbuvir*'s launch price, which I then situate in the wider organizational and political-economic dynamics shaping the innovation process – the central inquiry driving my study. Second, unpacking Gilead's internal pricing strategy through this interpretation of primary documents – rather than inference from secondary sources – allows a firmer consideration of the competing answers for the prices of new drugs reviewed in chapter 1. Finally, Gilead's pricing strategy would be a crucial determinant behind the effectiveness of *sofosbuvir*'s deployment in health systems, which in turn shaped the distribution of risks and rewards in the innovation process and public health outcomes (which provides data to answer my second research question).¹⁷⁹

Data from the US Senate Investigation shows that Gilead converted its position in the innovation process – as an acquisition specialist and end-stage owner of a pharmaceutical asset – to maximize its accumulation of capital. To seize this opportunity, Gilead (1) used the price of the existing standard of care for hepatitis C as a reference that served as a pricing floor, (2) evaluated the potential of competitors to erode accumulation, and (3) made a social and political estimation (through survey-based market research as well as interviews) of the upward limits of price that buyers would be willing to pay for *sofosbuvir*'s improved therapeutic value. Each of these factors ultimately pointed Gilead to a price of \$84,000 for its initial *sofosbuvir*-based regimen and set the

¹⁷⁸ I triangulated the data in the US Senate investigation with interviews and observation at meetings where drug pricing was discussed. Interviews 8, 16, 25, 31, 37 contributed to this understanding.

¹⁷⁹ Two major factors that can negatively affect the deployment of a medicine were not at play with *sofosbuvir*-based therapies: treatment complexity and health system capacity. Where many treatments can be complex, due to multiple doses per day and constant management of dosage level and side effects, *sofosbuvir*-based treatments comprised a once-a-day pill with few side effects (Ward and Mermin 2015). Where many health systems might not have the trained doctors and nurses to provide the medicine, most US and Europe systems had the requisite workforce (even in the case where there were not enough liver specialists, primary care doctors could be trained to provide a treatment that is simpler in many ways than treating diabetes or high cholesterol, given the ease of uptake). Price, then, was the driving factor for the deployment and public health outcomes realized in this case.

baseline for its eventual \$94,500 price for their *sofosbuvir*-based combination therapy.¹⁸⁰ *This pricing strategy culminated the pricing escalator highlighted in the prior chapter – with the prices of the prior standard of care serving as the floor (‘reference price’) upon which the company estimated the amount that health systems would be willing to pay in exchange for improved therapeutic outcomes.* Gilead considered this pricing strategy over the course of 2013, with a senior leadership group called the Global Pricing Committee meeting with IMS, a consulting group. In this section, I describe each of these three factors before considering their implications for our understanding of the drug pricing and innovation process.

Table 5.1 Key factors in Gilead’s pricing strategy

Pricing factor	Gilead’s consideration
Reference price of existing standard of care	- <i>Telaprevir</i> regimens typically came between \$80,000-96,000 total because of the long course of interferon and ribavirin. <i>Sofosbuvir’s pricing would be based on using this as a reference price from which to estimate what more health systems might pay in exchange for improved outcomes.</i>
Position of potential competitors	- Gilead believed that charging a lower price would enable future competitors to erode potential revenue and also erode their own ability to charge higher price for future combination therapies for hepatitis C. <i>Anticipation of competition in this case served to cement Gilead’s price floor.</i>
Estimation of buyers’ assessments of price and value of <i>sofosbuvir</i> therapies	- Buyers surveyed by Gilead initially indicated that they would not restrict access in the \$85,000-\$95,000 range, but would restrict at prices above that range. Multiple stakeholders, such as patient groups, indicated that budgetary pressures and the potential for access restrictions could however be triggered even at lower price points. <i>This evaluation gave Gilead a sense for the upward limits on what health systems could bear in exchange for ‘value’.</i>

5.1.1 The baseline: a reference price from the existing standard of care

The guiding framework for Gilead’s pricing approach relied on an assessment of the pricing of existing standards of care for hepatitis C at the time. From the outset, Gilead used the prices of the existing standards of care as a baseline from which to compare potential options for their *sofosbuvir*-based regimens (United States Senate, Committee on Finance 2015:33). Though

¹⁸⁰ As a reminder, Gilead’s initial wave of *sofosbuvir* would require interferon and ribavirin for 12 weeks but its ‘wave 2’ of *sofosbuvir-ledipasvir* (trade name Harvoni), would eliminate the need for interferon and ribavirin. It would ultimately be the first single-daily oral pill approved to cure hepatitis C (Kowdley et al. 2014).

this framework appears throughout Gilead's internal corporate deliberations, I use one example as illustrative of their assessment.

In a March 2013 briefing presentation with senior vice presidents at the beginning of deliberation, Gilead reviewed the pricing landscape of the standard of care therapies. In 2011, two 'first-generation' anti-viral therapies had been launched that were used in combination with the original *interferon* based regimens: Vertex's *telaprevir* and Merck's *boceprevir* (Chaplin and Dusheiko 2012).¹⁸¹ With fewer side effects, *telaprevir* had been the leading medicine of the two with more widespread use (Chaplin and Dusheiko 2012). In their model, Gilead deemed *telaprevir*'s price to be \$55,000 based on their scan of the prices Vertex was charging at the time (early 2013). *Telaprevir* still required an average of 9 months of ribavirin and the injectable treatment *interferon* (manufactured by Roche) as part of a complete regime. Adding this nine-month cost of *interferon* and *ribavirin* (\$28,000) to the price of *telaprevir* meant an average total price of \$83,000 for the existing standard of care at the time (United States Senate, Committee on Finance 2015:33). This pricing floor can be viewed as a cumulative effect of previous increases in prices for hepatitis C medicines (i.e. the pricing escalator).¹⁸²

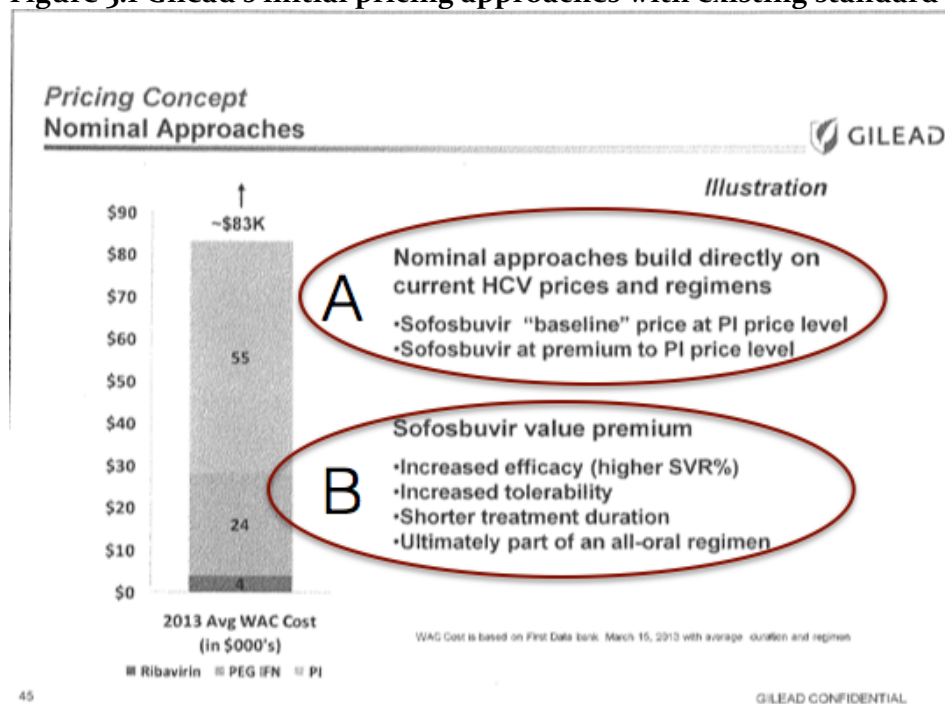
As Figure 5.1 demonstrates, Gilead's executives considered this ~\$83,000 price point to be a 'baseline' from which to then consider *sofosbuvir*'s 'value premium' that could enable Gilead to charge a higher price. They highlighted four key features of *sofosbuvir* that they believed could be used to justify this 'value premium' – the higher cure rates ('SVR' – sustained virologic response), increased tolerability (given few side effects compared to *interferon*), shorter treatment duration (only 3 months of treatment compared to an average of 9 months meant more patients would be able to begin and complete the regimen), and finally 'part of an all-oral regimen' (removing the need for *interferon* altogether) (United States Senate, Committee on Finance 2015:1349-1351).

¹⁸¹ Both of these compounds attacked the NS3/4 protease in the hepatitis C virus, making them less potent inhibitors than *sofosbuvir*, which attacked the NS5b polymerase. These earlier medicines, which also required the toxic *interferon* regimens, were phased out within 2 years, with the advent of *sofosbuvir*-based therapies.

¹⁸² The price of the *telaprevir* regimen itself was a product of the political-economic dynamics illustrated in this dissertation. Though the US Senate report did not have Vertex's internal documents, Gilead's internal documents indicated that Vertex had used the prices of the prior *interferon* and *ribavirin*-only regimens as a floor from which to estimate the 'value premium' of their *telaprevir* treatment. Observation of a presentation on drug pricing by a Vertex executive at the HEPDART conference supported this view. Vertex's prices combined with Roche's annualized price increases between 2003 and 2011 on their *interferon* and *ribavirin* treatments to produce a total regimen price at \$83,000 in 2013, when Gilead began deliberating on their *sofosbuvir*. Later in section 5.3, I illustrate how such price increases function to meet shareholder expectations for large established companies like Roche and Gilead.

Gilead's executives then sought to estimate the upward limits of what this value premium could be by turning to a consulting company – IMS – to survey payers to understand how much they would be willing to pay for improved therapeutic outcomes. I return to this assessment in section 5.1.3.

Figure 5.1 Gilead's initial pricing approaches with existing standard of care



Caption: Gilead's initial pricing approaches "build directly on current HCV prices and regimens" (A) with the company considering it as a baseline from which *sofosbuvir*'s higher quality could accrue (B) a "value premium" at a higher price (ovals and letters added), which they mapped out in subsequent slides.

Source: United States Senate (2015:1348)

5.1.2 The position of potential competitors

Gilead also took into consideration the position of competitors with hepatitis C compounds expected to be approved in the near-term (1-2 years). Though analysts expected *sofosbuvir* to be the compound with the best treatment outcomes, Gilead predicted two ways in which competitors could potentially diminish their revenue gains and considered how their pricing strategy could prevent this from happening.

One competitor Gilead examined closely, AbbVie, anticipated getting FDA approval on a regimen in the year following Gilead's launch of *sofosbuvir*. AbbVie's regimen would contain multiple compounds and be free of the toxic *interferon*, much like Gilead's planned second launch

series (dubbed ‘wave 2’) in which *sofosbuvir* would remain the backbone but be supplemented by another anti-viral (United States Senate, Committee on Finance 2015:46). Thus, AbbVie’s treatment regimen presented competition to later waves of Gilead’s *sofosbuvir*-based regimens. Because AbbVie might beat Gilead’s wave 2 regimen to approval, Gilead’s senior leadership and IMS consultants believed that Gilead’s wave 1 pricing (of *sofosbuvir*) – as the first curative compound to be approved - needed to set a strong baseline (United States Senate, Committee on Finance 2015:47). Otherwise, AbbVie could set a lower price point, thereby forcing Gilead to enter at AbbVie’s price point and depressing their revenue opportunity in Wave 2.¹⁸³ Gilead noted that pricing at \$60,000 would likely mean they would be “very unlikely to face any access issues” *but* the company would not be “realizing a substantial revenue amount and achieving more than an \$80K Wave 2 price will be unlikely, eroding shareholder value” (US Senate Finance Committee, p. 47). In other words: a low price would mean a better public health outcome, but it would hurt their ability to use it as a “high floor” to set the price of both their competitor’s and their own combination regimens. With revenue foregone, shareholder gains would be “eroded”. Gilead ultimately followed precisely this approach to set its “wave 2 pricing” of *sofosbuvir*-based regimens (*sofosbuvir* + *ledipasvir*) at \$94,500, using its “wave 1 pricing” floor of \$84,000 as a useful baseline.

Furthermore, Gilead feared that if they priced their *sofosbuvir* compound ‘too low’, other companies could then ‘pair’ *sofosbuvir* with their own compound and diminish Gilead’s revenue potential. For example, Bristol Myers Squibb (BMS) expected to enter the market with a potent viral inhibitor, *daclatasvir*, which would not be a stand-alone therapy but rather would need to be paired with *sofosbuvir* to realize higher cure rates (United States Senate, Committee on Finance 2015:49). Gilead feared that health insurers and public health systems might choose to pair *sofosbuvir* with *daclatasvir*, thereby limiting Gilead’s pricing potential for their own wave 2 combination regimen.¹⁸⁴ By ‘breaking-up’ Gilead’s combination *sofosbuvir*-based therapy, BMS would instead take a cut of the potential market.

Rather than forcing prices downward, these competitive dynamics, served to *cement*

¹⁸³ IMS laid out this possibility in stark terms: “If AbbVie’s 3-DAA comes to the market before (Gilead’s) Wave 2, it will become the standard of care (SoC) and Wave 2 will not be able to command a premium over it if equal market access is the goal” (United States Senate, Committee on Finance 2015:1451).

¹⁸⁴ In July 2013, Gilead’s pricing team warned the company’s senior leadership: “further consideration of BMS strategy has emphasized the possible risk of *daclatasvir* being used to break-up the *sofosbuvir* STR (single-therapy regimen) if a significant value capture opportunity is presented” (United States Senate, Committee on Finance 2015:1256)

Gilead's pricing floor, in order to 1) set a higher reference point for future market entrants and its own *sofosbuvir* combination regimens and also 2) to ward off competing companies from co-opting their *sofosbuvir* compound into alternative combination therapies.

5.1.3 Estimations of buyer's expectations of price and 'differential value premium'

A central piece to Gilead's deliberation comprised of evaluating the views of multiple players, focused primarily on the estimations and expectations of players across the fragmented and less-regulated US market from which Gilead expected to make a disproportionate share of its revenue.¹⁸⁵ As part of their work, IMS surveyed 90 payers in a double-blind fashion to identify the value they saw in an anonymized drug resembling *sofosbuvir*'s clinical attributes. Figure 6.2 below shows the breakdown between different US payers in IMS's survey – commercial health insurance plans, Medicare, and Medicaid – and the extent to which each would provide access for the medicines at different price points. The research gave IMS confidence about their use of the prior standards of care as a baseline, reporting to Gilead that the \$85-\$95,000 price range would be acceptable across a wide variety of health system payers.¹⁸⁶ Yet in their final recommendations, they also noted that other “softer factors must be considered” *beyond* their survey (United States Senate, Committee on Finance 2015:1249).

Discussions between IMS and multiple stakeholders pointed to these ‘softer’ factors, namely the potential for public outcry due to the high number of hepatitis C patients. In addition to the survey, IMS also prepared what they called a ‘heat map’ of the anticipated social and political responses that Gilead might face from multiple key groups– such as patient activists and the U.S. Congress – to different escalating price points (see Figure 6.3). This ‘heat map’ helped Gilead estimate the upward limits past which public outcry would be likely (United States Senate, Committee on Finance 2015:30). Strikingly, the rubric modeled for responses such as the probability of a “Congressional hearing”. Gilead's own stakeholder meetings confirmed these possibilities.¹⁸⁷ In 2013, for example, Gilead met with the Fair Pricing Coalition, a patient group

¹⁸⁵ The company used their launch US price as a reference point off which to negotiate prices in Europe and Japan, where predominantly government-financed health care systems typically have stronger regulating power (United States Senate, Committee on Finance 2015:59).

¹⁸⁶ Medicaid later would restrict treatment in this price range, as the numbers of patients requiring treatment exceeded their expectation. Furthermore, payers communicated that lower prices would ensure better access for *sofosbuvir* (see Figure 5.3).

¹⁸⁷ These cautions, however, were countervailed by a set of expectations from a powerful set of players: Wall Street investment analysts. In late October 2013, as Gilead prepared to launch *sofosbuvir*, Mark Schoenbaum – known as one of the top biotechnology investment analysts in Wall Street for the firm Evercore ISI – sent

which engaged senior leadership at pharmaceutical companies to provide input prior to a drug being released to the market. In their meeting, the group communicated their hope that Gilead would set a price of \$60,000, which represented the price of *telaprevir* without interferon or ribavirin (United States Senate, Committee on Finance 2015:101).¹⁸⁸

In closing their consultation with Gilead, IMS, citing \$80-85,000 per course of therapy as their recommended launch price range, summed up their thesis: “this price will allow Gilead to *capture value* for the product without going to a price where the combination of external factors and payer dynamics could hinder patient access to uncomfortable levels” (United States Senate, Committee on Finance 2015:1249). Taken from an array of players, these price estimates provided Gilead with an assessment of the upward limits of what health system buyers and the US political system could potentially bear.

5.2 Survey of US payers’ anticipation of access at various price points for *sofosbuvir*

PRICING AND MARKET ACCESS POTENTIAL

Payers believed that sofosbuvir in Wave 1 could command premium pricing to current products without significant access disadvantages

At what price would you provide...	COMMERCIAL	MEDICARE	MEDICAID
BETTER ACCESS FOR SOFOSBUVIR	<\$70K	<\$75K	\$65K - \$75K
EQUIVALENT ACCESS FOR SOFOSBUVIR	\$85K - \$100K	\$85K - \$94K	\$85K - \$100K
MORE RESTRICTED ACCESS FOR SOFOSBUVIR	\$85K - >\$170K	\$95K - >\$120K	\$100K - >\$140K
NO COVERAGE / OFF FORMULARY	Always covered	Always covered	>\$140K

BETTER ACCESS

- Payers indicate that they would prefer sofosbuvir over the current standard of care only if the regimen was less expensive
- Even if they recognize higher value in sofosbuvir, they would not prefer it and comment that it would in any case become the SoC over currently used treatments

MORE RESTRICTED ACCESS

- The majority of payers appeared to be more inclined to imposing restriction on sofosbuvir once the \$100K threshold was passed
- It must be noted however, that payers indicated that for price points slightly over \$100k, they would impose a “soft” PA, that is, they would simply ask prescribing docs why they would not use current SoC instead

1469

Sofosbuvir PAMA Assessment – SVP Briefing
39
ims consulting group

Caption: Both Medicare and Medicaid show a willingness to cover *sofosbuvir* at prices greater than \$85,000, increasing Gilead’s confidence on their preferred price range. (US Senate Finance Committee, p. 1469).

an email to Robin Washington, Gilead’s Chief Financial Officer (and a member of the company’s pricing committee), with the results of his own research. Schoenbaum had surveyed 203 investment analysts to ask them “where do you think GILD (Gilead) will price 12 weeks of single-agent sofosbuvir”? The average: \$85,400 (United States Senate, Committee on Finance 2015:1836).

¹⁸⁸ The Fair Pricing Coalition (FPC) believed that Gilead’s *sofosbuvir*’s price should reflect the large volume increases compared to prior therapies. The FPC director, Lynda Dee, had already communicated this view at the FDA review meeting for *sofosbuvir*: “I mean, if the price of *telaprevir* and *boceprevir* I think is already exorbitant. I mean, if you could prove it even close to what those drugs are, I think that you would be reasonable under the circumstances, and you’d still make a fortune. The volume that you’re going to get for this is I think its outstanding” (United States Senate, Committee on Finance 2015:101)

Figure 5.3 Gilead's assessment for potential stakeholder responses to *sofosbuvir*'s pricing

Aside from payer access and physician demand, there are a number of softer issues that could affect Gilead's final pricing decision



Stakeholders	Wave 1 Regimen	\$60,000	\$70,000	\$90,000	\$105,000	\$125,000
	Wave 1 SOF product (12 wks)	\$50,000	\$60,000	\$80,000	\$95,000	\$115,000
	Wave 2 FDC (8 wks or 12 wks?)	\$70,000	\$80,000	\$100,000	\$115,000	\$135,000
Payers	Likelihood of applying directly observed therapy due to high price	Unlikely	Possible	Possible	Likely	Likely
Physicians	Likelihood of delay treatment of GT-1 TN patients due to pricing	Unlikely	Possible	Possible	Likely	Likely
	Likelihood of losing some KOL endorsement/support as price too high	Very Unlikely	Unlikely	Possible	Likely	Likely
	Likelihood of getting rejection on TE patients and delay treatment for all due to misconception of restriction for SOF	Possible	Possible	Possible	Possible	Possible
Patients and Advocacy groups	Likelihood of AHF, FPC and other advocacy groups reacting negatively to price, and affecting public opinion	Likely	Likely	Very Likely	Very Likely	Very Likely
	Higher out-of-pocket costs (not offset by patient support) could drive patient choice away from SOF, especially AbbVie has great patient support programs	Very Unlikely	Very Unlikely	Unlikely	Unlikely	Possible
	Likelihood of AHF, FPC and other advocacy groups promote AbbVie products due to the relationship and lower price	Unlikely	Unlikely	Possible	Possible	Likely
Treatment Guidelines	Likelihood of AASLD develop treatment pathway to prioritize (staging) patients (per KOLs or/and professional community request)	Possible	Possible	Possible	Possible	Possible
	Likelihood of a "price mention or asterisk" in AASLD (per KOLs or/and professional community request)	Unlikely	Unlikely	Possible	Possible	Likely
Others	Likelihood of public outcry if SOF revenue exceed \$2B as government trying to control healthcare cost	Possible	Possible	Possible	Likely	Very Likely
	Likelihood of a letter from congress on SOF price	Possible	Likely	Likely	Likely	Likely
	Likelihood of a congressional hearing if SOF revenue exceed \$2B	Unlikely	Unlikely	Unlikely	Unlikely	Possible

Caption: Gilead attempted to assess the severity of negative responses at upward limits of the pricing range. For example, they anticipated "likelihood of a letter from congress on SOF price" at even \$70,000 for sofosbuvir, and "likelihood of public outcry if SOF revenue exceeded \$2B" at a price point of \$105,000.¹⁸⁹

Source: (United States Senate, Committee on Finance 2015:30)

On November 23, 2013, just two weeks before the FDA's decision date and likely approval for *sofosbuvir*, Gilead's senior leadership arrived at their price: \$84,000 (United States Senate, Committee on Finance 2015:57).¹⁹⁰ Ten months later, Gilead would launch its *sofosbuvir*-based combination therapy (which eliminated the need for *interferon* in all hepatitis C patients) at the price point of \$94,500 – meaning that Gilead's estimation of the 'value premium' for *sofosbuvir*-based treatments compared to the prior standard of care would be ~\$11,500 (see ~\$83,000 price point referred to in section 5.1.1). The three considerations described above guided them towards

¹⁸⁹ Gilead's initial revenue in 2014 from *sofosbuvir* exceeded \$10 billion at a price of \$84,000 .

¹⁹⁰ Why the precise price of \$84,000 for the launch price of the initial *sofosbuvir* treatment? John Martin, Gilead's CEO noted that the per-bottle price of \$28,000 (\$84,000 per three months divided by 3 = \$28,000/month) would be "easy from the press release, from 28 days and \$28,000"(United States Senate, Committee on Finance 2015:57). Gilead's other senior leadership concurred on the email chain, figuring that \$1,000 a day for the cure would make for an easy marketing push.

this price point, as it (1) was comparable to the existing standard of care given the ‘added value premium’, (2) provided a high baseline price from which to prevent competitors from eroding returns, and (3) came within the upward limits of the range the company forecasted would be acceptable to health systems in exchange for improved therapeutic outcomes.

Telescoping out from the close account of these three rationales, we can juxtapose Gilead’s pricing strategy with competing economic claims on drug prices, as well as situate it in the wider context of the innovation process. Notably, Gilead never considered their investments in research and development in the pricing process, and the ‘value’ of their therapies was never objectively defined or algorithmically calculated. The three factors I outlined converged on Gilead’s singular rationale for pricing: to maximize their opportunity to *grow* through *sofosbuvir*-based regimens. Their use of monopoly power in searching for this maximum price point, however, was situated in the broader political-economic dynamics of the innovation process driven by financialization. The use of the reference price (from the existing standard of care) and their estimation of the differential value that health systems would be willing to pay reinforced the *pricing escalator* that had previously mobilized speculative capitals behind Pharmasset. Furthermore, this pricing strategy underscored Gilead’s role in this chain of speculative actors – as an acquisition specialist betting on intangible assets, based on their anticipation of charging prices that continue this value-based pricing logic.¹⁹¹ *Gilead’s launch price strategy served as a culmination of this escalator, another ‘step’ in a long upward trend.*

The pricing immediately spurred a crisis of treatment access and a contentious public debate over the value of new breakthroughs which landed on the front pages of multiple news media (Knox 2013; Pollack 2013). We turn to the dynamics of this crisis next.

5.2 The State of Public Health or the Triage State?

Gilead’s pricing shaped the extent to which *sofosbuvir*-based regimens would create an optimal public health impact for hepatitis C. In this section, I first describe how instead of universal access at a price deemed affordable, the ‘public health delivery state’ became a “triage state” as they 1) allocated significant budgets for a small number of patients, 2) rationed treatment

¹⁹¹ Gilead had used this value-based logic for the prices they assumed for *sofosbuvir* in their capitalization exercise in 2011 at the time they made their \$11.2 billion acquisition on Pharmasset. As I describe later in this chapter, Gilead’s accumulation of revenue from their pricing strategy would enable them to reproduce and fortify their position in the innovation process – using this accumulated capital to search for intangible assets on which to bet (and distribute earnings to shareholders in the form of buybacks).

to only the sickest patients with hepatitis C, and 3) deferred public health planning to eliminate the disease. I then illustrate these public health outcomes in the context of both the limits of countervailing powers of the state in drug pricing as well as limits of health economic algorithms used to justify ‘value-based pricing’. This account is based on health policy articles, media accounts, interviews¹⁹², drug spending database, and observations at meetings.

5.2.1 Turning to Triage

Health systems around the world responded to the price by allocating significant public funding to treat only a small number of patients while limiting access to only the sickest patients in the late stages of disease (Iyengar et al. 2016).¹⁹³ I focus this section on treatment access and spending on *sofosbuvir*-based regimens in the U.S., where a fragmented network of public payers are responsible for the care of a significant proportion of hepatitis C patients, particularly those experiencing social disadvantage (Chahal et al. 2015; Ward and Mermin 2015; H. F. Yee Jr 2015). Official estimates indicate that the US has over 3.2-4.7 million infected with hepatitis C, with public systems responsible for approximately 50% of this population, including veterans, incarcerated populations, low-income, Native American, and elderly patients (Edlin et al. 2015).¹⁹⁴ Taken together, the health systems responsible for these patients constitute a “health delivery state” (Khullar and Chokshi 2016), in which taxpayers finance the health of multiple populations, from patients over the age of 65 (Medicare), low-income patients and disabled (Medicaid), veterans (Veterans Affairs), Native Americans (Indian Health Service), and those incarcerated (state prison systems).

Three dynamics shaped patient and public health outcomes in the US from the development and pricing of *sofosbuvir*-based regimens. First, US health systems had to grapple with the significant budgetary expenses of treating even a small fraction of hepatitis C patients,

¹⁹² Interviews 2, 8, 16, 18, 22, 29, and 31 provided insight into the dynamics of treatment access.

¹⁹³ Across Europe, even publicly financed health systems with centralized negotiating power over drug prices placed restrictions on treatment due to the large numbers of potential patients seeking treatment (Chabrol, David, and Krikorian 2017; Gornall et al. 2016). In the UK, for example, the National Health Service restricted treatment for nearly two years after their launch to under 3,000 thousand patients, and then only expanded treatment to ~10,000 per year (Gornall et al. 2016). Though Gilead offered a license to generic companies to produce the medicine at approximately \$1,000 in low-income countries where the company did not expect to garner high sales in any case, the company restricted this license so that many middle-income countries with high hepatitis C burdens met difficult budgetary choices with limitations in treatment availability (Love 2014c; Momenghalibaf 2014)

¹⁹⁴ This wide estimate is due to the uncertainty created from the large number of undiagnosed patients who may be in their early stages of disease.

and the opportunity costs for spending in other areas of health and social concern. Second, in considering the budgetary consequences of these medicines, health systems responded with treatment access restrictions, forcing patients to wait for the medicines. Third, and finally, public health officials and policy-makers deferred the planning for an elimination-focused strategy for hepatitis C which in turn has supported the conditions for the long-term durability of the epidemic.

The first two dynamics are captured in Table 5.1, which summarizes the responses of various U.S. public health delivery systems in the two years after the launch of *sofosbuvir*-based treatments. Amidst financial and treatment access challenges, approximately 230,000 patients were treated with *sofosbuvir*-based treatments in 2014-2015 across these systems over the first two years of their launch, far less than the 1.6 to 2.4 million hepatitis C patients with publicly funded insurance.¹⁹⁵ I now map each of these two dynamics – budgetary pressures and treatment access – in detail and then turn to the deferment of public health planning.

¹⁹⁵ This comprised a significant share of the 400,000 patients Gilead has estimated for the entire US population, with the rest accessing the treatment through private insurance.

Table 5.2: US public health delivery response to sofosbuvir-based treatments, 2014-2015

Public health delivery system	Treatment restrictions?	Estimated hepatitis C population ¹⁹⁶	Treated hepatitis C population	Hepatitis C spending
Medicare	No, Medicare cannot legally restrict access nor can they negotiate with drug companies on pricing	350,000 (Hoadley et al. 2016; United States Senate, Committee on Finance 2015)	135,238 patients (CMS 2016)	\$12.15 billion (\$3.8 billion in 2014 and \$8.15 billion in 2015, at average price of \$90,000) (CMS 2016)
Medicaid	Yes, state programs restricted access to patients based on their stage of disease as well as substance use (alcohol, injecting drugs), with only the sickest eligible to receive the medicines. (Barua et al. 2015; Canary, Kleven, and Holmberg 2015)	700,000 United States Senate (2015) surveyed all US state Medicaid directors	51,512 ¹⁹⁷ Using United State Senate (2015) for 2014 data, and Center for Medicare and Medicaid (CMS 2016) drug spending dashboard	\$4 billion Using United State Senate (2015) for 2014 data, and Center for Medicare and Medicaid (CMS 2016) drug spending dashboard; \$1.2 billion in 2014 and \$2.8 billion in 2015
Veterans Affairs	Yes. In 2014-2015, patients waited for treatment in earlier stages of disease. In second-half of 2015, VA ran out of budget for hepatitis C, forcing patients to wait until 2016 (Graham 2016)	174,000 (Veterans Affairs 2014)	42,000 (Jan 2014 – March, 2016) (Veterans Affairs 2016) 5,400 veterans treated in 2014; (Kime 2015)	\$1.066 billion - 2014: \$370 million - 2015: \$696 million, 17% of their entire pharmaceutical budget *Congress appropriated \$3 billion for hepatitis C treatment in 2016 and 2017. (Graham 2016; Veterans Affairs 2016)
Departments of Correction (state prison systems)	Yes, rationed access based on length of stay in prison as well as cirrhosis staging	~106,000 (data from 41/50 states, estimated to be 10% of the entire prison population)	949 patients (.89% of the estimated total population of infected)	Atleast \$39.8 million in 2014, with no figure for 2015 All data in this row from Beckman (2016), which surveyed all 50 state DoCs
Indian Health Service (HIS)	Yes, because IHS has not directly funded hepatitis C treatment, patients seek care typically via Medicaid programs, which have restrictions (Leston and Finkbonner 2016)	National data is limited, one study estimated 120,000 positive (Edlin et al. 2015)	No direct treatment available (Leston and Finkbonner 2016)	No supplemental HCV budget; entire annual budget of HIS is \$4.6 billion (Leston and Finkbonner 2016)

¹⁹⁶ These estimates include diagnosed and estimated undiagnosed patients.

¹⁹⁷ 2015 data was reported in terms of prescriptions versus beneficiaries, with an estimated 105,695 prescriptions. If we assume an average of three prescriptions per patient (each prescription lasts one month for a three month regimen), this would indicate about 35,231 patients treated (CMS 2016).

First, covering all hepatitis C patients was estimated to take up a large share of the *entire* pharmaceutical budget for U.S. health systems, forcing a consideration of opportunity costs for other areas of health and social spending. One prominent study estimated that treating all hepatitis C patients in the US over 5 years would require \$136 billion to cover drug costs, of which \$61 billion would need to be paid by the government (Chahal et al. 2015). Even treating a small fraction of patients ultimately required significant allocations of new spending which represented large proportions of health system budgets. For example, the Veterans Affairs administration in 2015 ran out of funding for hepatitis C drugs in the second half of the year after spending nearly 17% of their entire pharmaceutical budget on *sofosbuvir*-based treatments (Flynn 2015; Graham 2016; 2016b). Public pressure in early 2016, stemming in part from two national news broadcasts devoted to the VA challenge, led the US Congress to allocate \$3 billion for hepatitis C treatment; advocates are still concerned that many may have to wait (Graham 2016).¹⁹⁸ US veterans suffered from high rates of hepatitis C primarily from blood transfusions and injecting drug use during the Vietnam War (Flynn 2015). The US Medicaid system, run by individual US states, spend \$4.0 billion during 2014-2015 to treat 7% of all hepatitis C patients (CMS 2016; United States Senate, Committee on Finance 2015). The state of New York, for example, spent 10% of their entire pharmaceutical budget in 2015 on hepatitis C (Goldberg 2016).

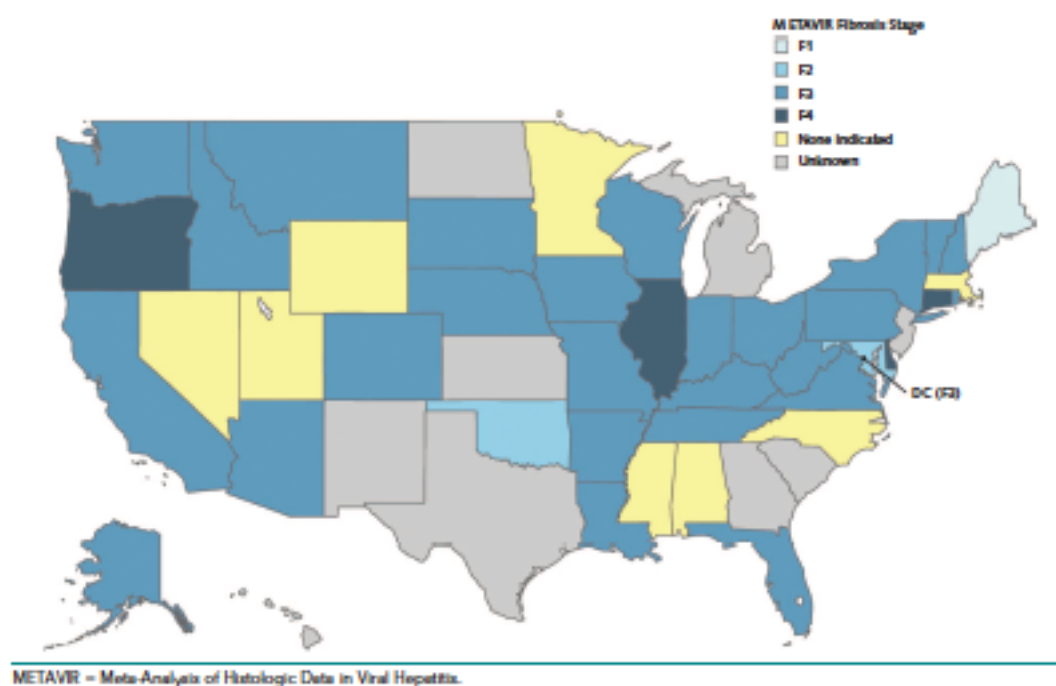
Second, in weighing these budgetary pressures, health systems restricted access to treatment, turning to a system of *triage* to contain costs. In the U.S. Medicaid program where individual states make determinations over spending allocations, a majority of states placed significant restrictions (see Figure 6.4) on *sofosbuvir*-based regimens (Barua et al. 2015; Canary et al. 2015; J. Walker 2015). Patients on Medicaid have been triaged for treatment largely based on two criteria: stage of disease and substance use (see Table 6.1). Most states restricted patients by the staging of their liver disease, allowing only patients with advanced fibrosis (medically categorized as those with F3 and F4 staging) to receive access (Barua et al. 2015; Canary et al. 2015).¹⁹⁹ Additionally, many states required that patients be alcohol and drug free in the one month to upwards of 6 months leading up to treatment. Most observers concluded that these

¹⁹⁸ Tricia Lupole, executive director of HCVets, a website run for veterans with the disease, shared in an interview with *Journal of Medical Association* (JAMA), “The fact is they don’t have the money to treat everyone despite what they’re promising.” (Graham 2016).

¹⁹⁹ 33/50 states instituted restrictions, including the largest states. F3 and F4 stage refers to late stage liver fibrosis (scarring of liver tissue), as compared to patients in earlier F0, F1, or F2 stages.

guidelines, which had no clinical basis, were set up as mechanisms by which to delay access and contain costs (Barua et al. 2015; Canary et al. 2015; Ward and Mermin 2015). In a study by researchers at University of Pennsylvania researchers found that nearly 50% of Medicaid patients were denied access because the medicines were deemed to not be a “medical necessity” or because “the patients tested positive for alcohol/drugs” (Re et al. 2016). These denials disproportionately fell on those populations most at-risk for worsening hepatitis C as well as transmission of the infection: low-income patients with histories of injecting drug use.

Figure 5.4 Medicaid requirements for treatment access by liver disease stage as of June, 2015



Note: The darker blue shades indicate the majority of states restricting access to late stages of liver disease (F3 and F4), 18 months after sofosbuvir-based treatments had been approved by the FDA. Source: (Barua et al. 2015)

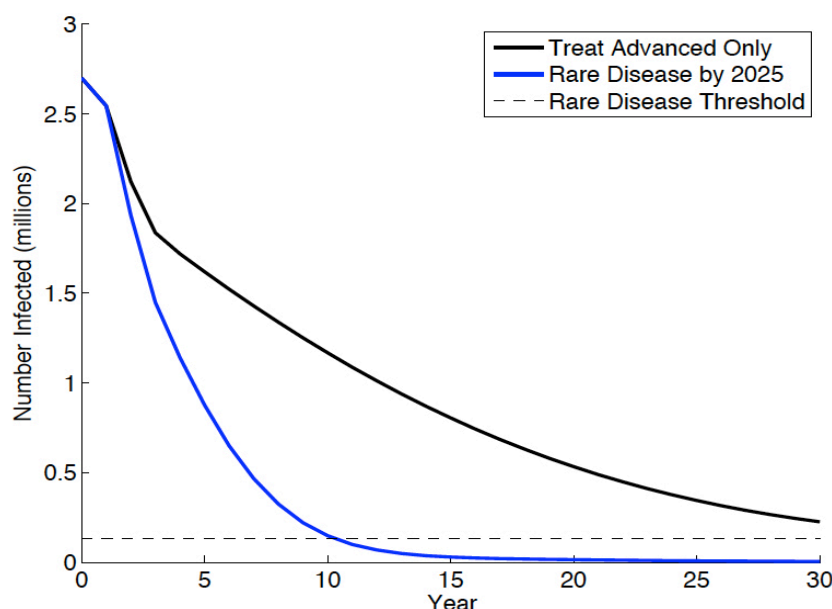
Beyond the US Medicaid system, these restrictions have impacted another crucial vulnerable population: incarcerated patients. The US prison system, which holds an estimated 15% to 25% of the entire hepatitis C population in the US, has provided treatment to less than 1% of its patients (Beckman et al. 2016; He et al. 2016). State prison systems are not mandated to receive a discount from Gilead, making their access challenges even steeper than other public systems (Ayer et al. 2016; Loftus and Fields 2016; United States Senate, Committee on Finance

2015). Restricting access in this population presents a major squandered opportunity for tackling the epidemic to this point, as prisons are often the only stable source of health care for these patients; after release, they are also at higher risk for transmitting the virus in the community (Barry-Jester 2015; He et al. 2016). This uneven use has presented challenges for providers and patients at the frontlines of care delivery. Caregivers described the predicament for doctors and patients in the journal *Journal of the American Medical Association (JAMA)*: “Earlier treatment can prevent advanced liver disease, but late-stage disease is needed to qualify for treatment: for a clinician, explaining this circular logic to a patient can be frustrating for both parties” (Leston and Finkbonner 2016:817).

These restrictions and budgetary pressures have converged on a third dynamic shaping the public health outcomes of *sofosbuvir*-based medicines: *the deferment of public health planning for hepatitis C elimination*. In a major national commission on viral hepatitis organized by the Institute of Medicine in 2016, experts concluded that eliminating the public health problem of hepatitis C was clinically possible but “would require near universal access to treatment, something that appears unfeasible given the current pricing and policy environment” (National Academies of Sciences, Engineering, Medicine 2016). The unfolding public health consequences of this deferred implementation are significant over the long-term. A modeling study performed by myself with colleagues compared the effect in the US of expanding treatment access and versus the ‘restricted’ strategy currently being deployed (Roy, Chokshi, Kissler, and Singh 2016a). Figure 6.5 demonstrates the differences in population-level outcomes over the next decade. Under an expanded access strategy, hepatitis C could be transformed from an epidemic to a rare disease, with less than 150,000 infected patients by 2025. But under a restricted scenario, more than a million people would still be infected. The virus would persist for decades longer.

Gilead’s pricing, therefore, created a set of stark challenges for the health delivery state. In the face of the prices for *sofosbuvir*-based medicines, a ‘Triage State’ allocated significant portions of their budget to treat a small fraction of patients, restricted treatment to contain costs, and deferred the implementation of a public-health centered plan to eliminate the virus in the population. This crisis of the Triage State in the case of *sofosbuvir*-based medicines was not an inevitable outcome; rather, it illustrated relations of power between drug manufacturers and the U.S. state that were one element in sustaining the mechanisms of financialization described thus far.

Figure 5.5 US hepatitis C epidemic under ‘rare disease by 2025’ versus ‘restricted treatment’ scenarios



Caption: A Markov model showing that treating all patients in the US with advanced liver disease in the next two years followed by progressively more patients in early stages of disease, especially among those who inject drugs, can make hepatitis C a rare disease by 2025, with under 200,000 infected persons as compared to restricting treatment to only those with advanced disease. Source: Roy (2016a)

5.2.2 Public-private powers and the limits of value-based pricing

As described in section 5.1, Gilead priced their therapies based on an estimation of the upward limits of what health systems could pay, using the pricing of the existing standard of care, *telaprevir*, as their key reference for the ‘value’ Gilead believed their therapies would command given *sofosbuvir*’s superior clinical attributes. This pricing strategy, designed to maximize Gilead’s revenue accumulation, was shaped by two dynamics contained within the innovation process. The first dynamic is the growing but contested use of ‘value-based pricing’ as a standardized algorithm deemed to objectively evaluate a therapy’s price for the ‘value’ it provides health systems. This logic of ‘value-based pricing’ is tightly affixed to a second dynamic, however: the limited countervailing power of the state vis a vis oligopolistic pharmaceutical businesses like Gilead. I describe each dynamic in turn to show how drug pricing is politically constituted within the innovation process.

The arguments over value-based pricing emerged and intensified in the months after the late 2013 launch of *sofosbuvir*. As Gilead’s pricing drew increasing scrutiny in 2014, the company’s

senior leadership countered with a repeated message, summed up in a Bloomberg Business interview with Executive Vice President Gregg Alton. “Price is the wrong discussion”, he asserted, “value should be the subject” (Barrett and Langreth 2015). Gilead’s executives and industry leaders, buttressed with evidence from health economic studies, communicated value in two ways.²⁰⁰ First, *sofosbuvir* provided a much higher cure rate at a price comparable to the prior standard of care for hepatitis C – this meant health systems were essentially paying similar or slightly higher prices (depending on the given health system and the price) as before for a much better health outcome. Second, not only could more patients be cured immediately, but by treating patients in their early stages, health systems could also save the downstream costs of progressive liver disease (Chahal et al. 2016; Tice et al. 2015). The annual medical expense for a patient in the F4 stage of liver cirrhosis, for example, was estimated to be \$20,000 due to complications and hospitalizations, and liver transplant costs exceeded \$150,000 (Van Nuys et al. 2015). These justifications of value had figured into Gilead’s pricing strategy, when the company and IMS gathered *subjective assessments* through interviews from a variety of stakeholders to estimate the highest price at which the drugs would present value for health systems in comparison to the existing standards of care at the time.

As health systems began to decide their responses to paying for and providing access to the therapies in 2014-2016, Gilead’s executives – and the wider health policy community – turned to a series of health economics studies regarded in academic and policy circles as an *objective assessment* of *sofosbuvir*’s value. In a series of eight major health economics papers²⁰¹ published in the two years after *sofosbuvir*’s launch (see Appendix D for the studies and a short technical summary), each affirmed the pricing of *sofosbuvir*-based treatments as ‘value-based’ using *comparative cost-effectiveness* methodologies.²⁰² These studies, with one prominent study funded

²⁰⁰ These value arguments from the pharmaceutical industry also adopt and co-opt the arguments made by the US government, in which the Affordable Care Act (‘Obamacare’) has attempted to shift health care systems from ‘fee for service’ (i.e. incentivizing number of tests and doctor visits) to ‘value-based payments’ (i.e. incentivizing improvements in health outcomes) (Obama 2016).

²⁰¹ These eight studies used slightly different assumptions and methods, but arrived at similar conclusions on *sofosbuvir*-based treatments (Chahal et al. 2015; Chhatwal et al. 2015; Leidner et al. 2015; Najafzadeh et al. 2015; Rein et al. 2015; Tice et al. 2015; Van Nuys et al. 2015; Younossi et al. 2016).

²⁰² I provide brief background in this footnote regarding the method, but see Chapters 2 and the Appendix D for a more expansive technical summary. Put simply, these studies calculated the difference in costs between the regimens divided by the difference in health outcomes (measured in QALYs, quality adjusted life years), to produce a cost-effectiveness ratio of dollars spent per QALY unit of health gain; if the dollars are below a certain threshold, the medicine is deemed to be cost-effective. These thresholds vary based on

by Gilead itself, were widely used in policy meetings and in the media as a rationale for Gilead's pricing. One economic modeling study summed up the commonly held finding: "treating HCV infection at early stages of fibrosis appeared to improve outcomes and to be cost-effective" (Chahal et al. 2016:65). The study also contained a caution, however, that would expose the rift between health systems and Gilead: though the treatments were cost-effective compared to prior therapies and could save billions in downstream medical expenses, this savings would be incurred at "substantial aggregate costs" that "may have implications for health care coverage policies and clinical decision making" (Chahal et al. 2015:65). This basic tension – between supposed savings and cost-effectiveness of the treatments in the long-run and the significant, near-term budgetary costs – exposed the limitations of conventional health economics studies in three ways.²⁰³

First, cost-effectiveness studies for *sofosbuvir* could not account for a major shifting political-economic variable: the rise in drug prices over time, or what I have illustrated to be the *pricing escalator* in the prior chapter. This trend, clearly demonstrated in hepatitis C (see Figure 5.7), 'up-shifted' the prices at which comparative value assessments were being made. While the price of interferon regimens was \$19,000 in 1998, they had jumped to \$32,000 for a modified version by 2002 (United States Senate, Committee on Finance 2015). With the advent of telaprevir in 2011, the price leaped again, with regimens now crossing \$80,000 per patient (Vernaz et al. 2016). Each price point was justified by companies on the basis of the progressive improvements in health outcomes. The doctor and policy analyst Peter Bach (2015), has pointed out the challenge this raises for analyzing prices using existing value frameworks: "expensive drugs can still seem deceptively cost-effective, because of the long upward spiral we have seen." This upward spiral reflects the cumulative effects of the financialized mode of drug development, as these increasing prices and market valuations for hepatitis C helped mobilize speculative capitals in the prior chapter.

Along with the pricing escalator, the limits of cost-effectiveness analysis are also related to a second factor: an increased number of patients eligible for treatment. As was the case with *sofosbuvir*-based treatments, better clinical outcomes with a new therapy expands the number of

the preferences of a given health system and country. For example, the NHS in the UK is typically 'willing to pay' \$20,000-\$30,000 for an additional QALY.

²⁰³ I provide a broader analysis and critique of the value argument in chapter 6, pointing to the inability of such arguments to account for the difference between value creation and value extraction, and even value destruction. Here I share the basic arithmetic problems with using such health economics studies in a context of rising drug prices.

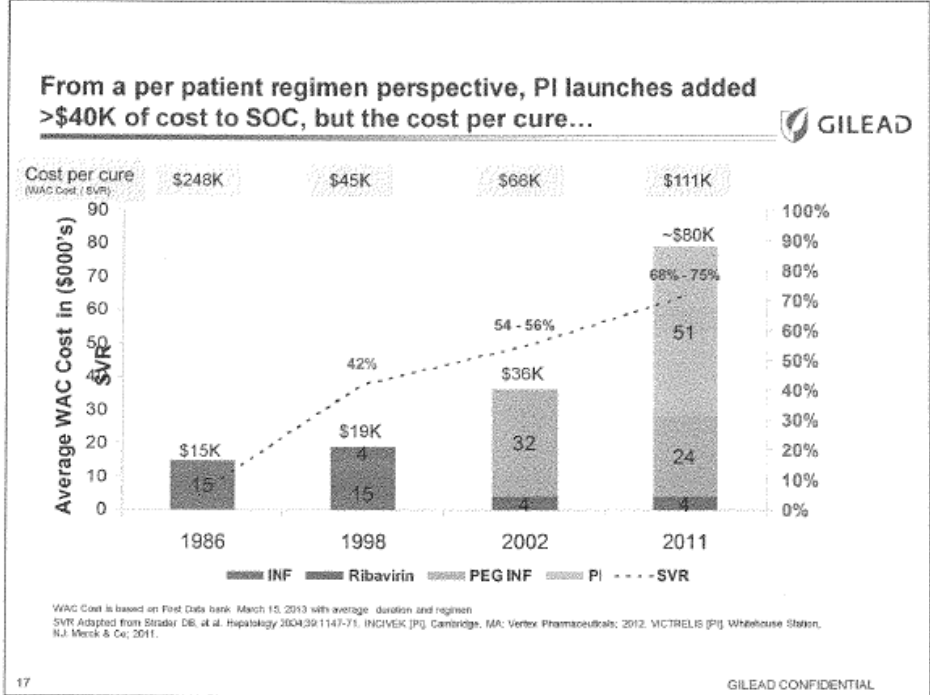
patients who can benefit – in other words, the ‘volume’ of patients grows (Reinhardt 2015). With many more patients seeking treatment at per-unit prices that are higher than before, prices that are deemed ‘cost-effective’ buckle the budgets of health systems. Gilead anticipated this explosion of cost for health systems (See Figure 5.7), forecasting dramatic increases in hepatitis C spending in 2014 and onwards with the launch of their medicines. This second factor in turn created the problem of social opportunity costs for governments highlighted in section 5.2.1, with decision-makers weighing whether hepatitis C spending would displace investment in other health or social purposes (Reinhardt 2015). Though studies analyzing *sofosbuvir*’s value provided a justification for Gilead’s pricing using widely adopted cost-effectiveness methodologies, they could not resolve the challenges posed by higher prices and social opportunity costs.

Finally, the ‘savings’ argued to accrue to health systems through early treatment was based on a set of illusory assumptions. The savings were measured in these studies over 30 to 50 year time horizons – but governments make budgets in much smaller time horizons, making it difficult to allocate significant new spending to single therapeutic areas for the purpose of realizing savings decades later. More importantly, *the costs of treatment far exceeded the anticipated savings accrued from sofosbuvir*.²⁰⁴ The study by Chahal, for example, found that treating all patients in the US even at a 46% discount from Gilead’s launch price would require \$29 billion and result in savings of \$3.3 billion versus treating only patients in their late stages of disease.²⁰⁵ The treatment regimen did represent a value for patients as a curative therapy, but these health economic studies attempted to justify its price as a reflection of value in isolation of the political realities of budgets and public health.

²⁰⁴ Joseph Dumit, in his work on pharmaceutical consumption, has noted that the ‘downstream savings’ argument for early treatment with high priced medicines ignores the reality that patients who receive treatments live longer, sustaining their possibility as a target for further pharmaceutical intervention and spending (Dumit 2012a; 2012b). He makes this provocative point to illustrate that the humanitarian argument for treating patients early of disease is perhaps the most reasonable justification, rather than the economic savings argument.

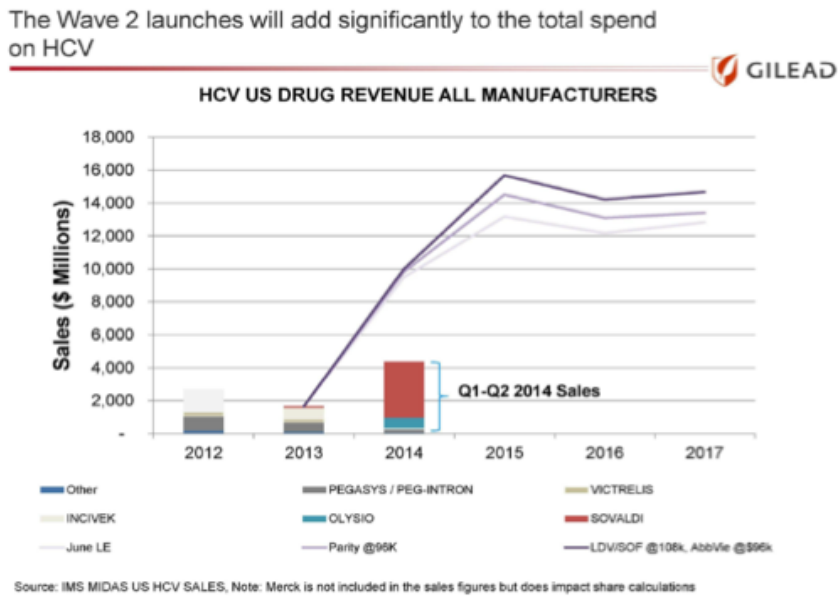
²⁰⁵ Chahal et al (2016) notes, “For budgetary considerations, if only 50% of eligible patients with HCV genotype 1 were to be treated with sofosbuvir-ledipasvir during the next 5 years, the cost of drugs in the United States would be \$53 billion at current prices. Many payers negotiate prices, as has been seen with exclusivity deals with drug manufacturers. If a mean 46% reduction in drug prices occurred, the cost of treating 50% of patients with HCV genotype 1 during the next 5 years could be as high as \$29 billion, partly offset by \$3 billion in savings in the management of chronic HCV and advanced liver disease.”

Figure 5.6 Historical price escalation from 1986 interferon to 2011 *telaprevir* regimen



Caption: The upward ladder of price increases on prior hepatitis C medicines shifted the entire valuation of Gilead's *sofosbuvir*-based regimens. Source: US Senate Finance Committee (2015:1320)

Figure 5.7 Sales of HCV drugs expected to dramatically increase with new patient population



Source: US Senate Finance Committee 2015:1620)

These debates over ‘value-based pricing’ were ultimately tied to a second dynamic: *the limits of public health systems to negotiate and regulate drug pricing in the face of publicly-granted monopoly power*. Gilead was not operating in a free and competitive market of textbook fame; rather, as Gilead entered the hepatitis C market in late 2013 and onwards, the patents for *sofosbuvir*-based regimens granted by the US Patent and Trademark Office (USTPO) assured protection until 2028 (Reinhardt 2015).²⁰⁶ This protection enabled Gilead to price free from competitive pressures at the time of its launch. The entry of two companies with curative hepatitis C regimens (AbbVie in 2014 and Merck in 2016) did eventually lead to modest price competition, with Gilead dropping its prices to certain public systems like the VA and some Medicaid states to below \$50,000 (Crow 2016b; Dabney 2016).

Yet a major national commission in the US of hepatitis C experts concluded in March of 2017 that even a price of \$40,000 per patient would prevent a public health oriented elimination strategy from being employed (National Academies of Sciences, Engineering 2017). Under such a scenario, the commission found that 240,000 patients on Medicaid would be treated over 12 years at a cost of ~\$10 billion, far short of the nearly 700,000 patients infected with hepatitis C on the program currently. The commission predicted, “It is unlikely that market forces alone will lower the prices of these drugs sharply or quickly enough to meet the targets set. The goals described depend on prompt, large-scale treatment of hepatitis C, and the price of these drugs is a major obstacle to unrestricted treatment, especially for institutions of limited means such as the prison system and state Medicaid program” (National Academies of Sciences, Engineering 2017:7). In their report, the commission concluded that alternative methods of negotiation between the US government and manufacturers would be needed to overcome the pricing obstacle.²⁰⁷

²⁰⁶ Pharmasset originally patented the *sofosbuvir* compound in 2008, with patents from USTPO lasting 20 years from the time, including clinical testing time (World Health Organization 2016). This followed from their 2004 patent on the pre-cursor to *sofosbuvir*, PSI-6130.

²⁰⁷ The commission proposed that the government engage Gilead in a negotiation in which a winning company would receive compensation in exchange for a license; this license would then be used by a third-party manufacturer to produce generic versions of hepatitis C treatments. At the roughly \$200 per patient for a three-month regimen it would take for a generic supplier to produce the medicine and retain a sustainable profit margin (Hill, Khoo, and Fortunak 2014), such a strategy would provide for universal treatment to the Medicaid population at a cost of \$140 million in addition to compensation provided the prior patent holder. The commission determined that this generic licensing and production approach was the only way for public health targets to be realized over the next decade. The report considered several ways to compensate the patent holder, estimating a potential compensation deal in the arena of \$2-3 billion,

This prediction was founded on a long-run observation: the limits of public health delivery systems in the US in exercising counter-vailing power in the face of state-granted monopolies. For example, the Medicaid program for low-income populations is a joint state-federal program, with individual states charged with allocating spending for pharmaceuticals and the federal government splitting the costs; the fragmentation of the Medicaid market into 50 separate states diminishes their negotiating leverage (Obama 2016; Paradise 2017).

The US Medicare program has faced a different challenge: it was explicitly barred from negotiating pricing with companies upon legislative passage of its prescription drug plan in 2003 (Oliver, P. R. Lee, and Lipton 2004). The rationale at the time, heavily influenced by the PhRMA lobby group, was that ‘the market’ would lower prices with private prescription insurance plans competing to attract beneficiaries and translating this into market power with which to negotiate with manufacturers – with taxpayers financing the scheme (Oliver et al. 2004). Yet studies have shown that Medicare has not been able to gain discounts from the launch prices set by companies (Bach 2009; Bach and McClellan 2005; Gellad et al. 2008), and the case of hepatitis C appears to demonstrate this point: Medicare spent \$90,000 per patient for *sofosbuvir*-based regimens at a total cost of \$12.15 billion in 2014-2015 (CMS 2016).

Furthermore, though the US Center for Medicare and Medicaid Services under President Obama raised the possibility of using the ‘March-in rights’ rule contained in the Bayh-Dole Act, in which the government grants a license to a third-party manufacturer in cases where publicly funded technologies are necessary to address a public health concern, the provision has never been exercised in the 37-year history of the law (Kesselheim 2011; Rai and Eisenberg 2002). This record of avoidance has continued with the case of hepatitis C (Silverman 2016d).

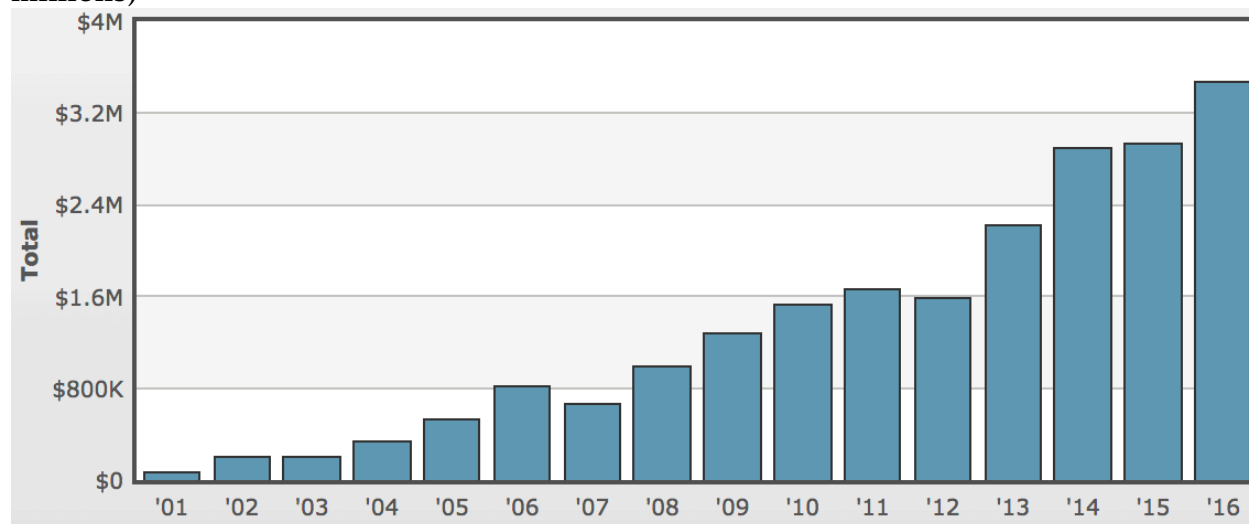
The limited countervailing power of the state has been shaped in part by the conversion of Gilead’s accumulated capital into lobbying government officials responsible for policies on drug pricing and intellectual property. For example, while Gilead’s lobbying expenses grew steadily with their HIV revenues during the 2000s, their expenses more than doubled (see Figure 5,9) with the advent of *sofosbuvir* from \$1.59 million in 2012 to \$3.48 million in 2016 (OpenSecrets 2017). Publicly available records show that Gilead used lobbying groups with prominent officials from both major political parties.²⁰⁸ According to federal disclosure reports, Gilead gave their lobbyists

since companies like Gilead are not gaining unrestricted access to neglected markets like Medicaid at current prices (National Academies of Sciences, Engineering 2017).

²⁰⁸ These officials included Arshi Siddiqui, a former senior policy advisor to House Minority Leader Nancy Pelosi; Josh Lamel, former legal counsel to Senate Finance Chairman Ron Wyden; Ryan Long, former chief

the job of influencing “hepatitis C policies” and providing “education on hepatitis C issues” (Demko 2014). In the fall of 2014, as scrutiny increased on Gilead’s pricing, the company hosted a forum, “Curing hepatitis C – the patient’s perspective”, for legislative staffers at the Rayburn House Office building in Washington DC (Demko 2014). A hepatitis C doctor, who earned \$20,000 in payments from Gilead, joined a Gilead vice president and a hepatitis C patient to argue for the ‘value’ of hepatitis C medicines (Demko 2014).²⁰⁹ Such lobbying by Gilead is part of the much larger efforts by the pharmaceutical industry, which spent more than any industry - \$2.3 billion – to influence key decision-makers in Washington DC between 2006 and 2016 – with two lobbyists per member of Congress (Chon 2016).

Figure 5.8 Gilead’s lobbying expenses on US federal decision-makers, 2001-2016 (in millions)



Source: Open Secrets database (2017)

In sum, section 5.2 illustrates the patient and public health consequences of this relationship of power between state-financed health systems and Gilead Sciences towards drug

health counsel for the House Energy and Commerce Committee under Republican leadership (Demko 2014).

²⁰⁹ The ranking Republican senator on the Senate VA committee, Richard Burr, later stood up for Gilead and its pricing, arguing, “innovation is expensive...I think the one thing we agree on is we don’t want to give up on innovation.” He continued that instead of attacking prices, the VA should look at how much could be saved in the long-term, “I believe the price of this particular drug should be look at on the macro level.” In this exchange with a media outlet covering veterans issues, Burr echoed the two lines – ‘risk’ and ‘value’ – used by Gilead and the industry to justify its prices. Burr made these arguments in multiple Senate testimonies and public interviews; in 2014, Gilead also donated \$5,000 to Burr’s political committee, the maximum allowable donation (Kravitz 2016; Tritten 2014).

pricing. In the face of Gilead's prices, health systems allocated significant spending to treat a small fraction of patients, relying on treatment restriction criteria to limit the budgetary pressures posed by the cost of treating large populations of hepatitis C patients. Additionally, public health planning for hepatitis C elimination has been deferred, with government health systems failing to exercise countervailing power to negotiate lower prices with Gilead. These prices have been justified by Gilead based on their 'value', derived from health economic studies that fail to account for the long-run increase in the prices of prior hepatitis C medicines. As we observed in chapter 4, this pricing escalator was linked to the mobilization of speculative capital behind Pharmasset and fueled Gilead's valuation of *sofosbuvir* in their acquisition of Pharmasset.

For advocates of the value-based pricing argument, however, these increasing prices were the primary incentive for the development of a curative therapy: paying more, in this view, would mean more curative therapies like *sofosbuvir* would be developed by the pharmaceutical industry (Kliff 2014).²¹⁰ The extent of this claim, however, would be conditioned by the very speculative and shareholder-driven processes driving the pricing escalator documented thus far. I now turn to tracing these processes into Gilead's business strategy as they accumulated capital from hepatitis C sales.

5.3 Gilead's Conondrum: The Limits of a Cure for Shareholder-Driven Growth

Rather than experiencing durable success in the eyes of financial markets with its hepatitis C sales, Gilead in turn faced another episode of crisis shaped by the shareholder-driven growth treadmill: whereas shareholders value assets that provide continuous and near-term *growth*, *sofosbuvir*-based medicines represent a cure which promises to reduce patient numbers over time. The extractive strategies driven by Gilead's shareholders were exacerbated by the company's ownership over a 'curative asset' - even with \$19 billion in sales for hepatitis C just in 2015 and nearly \$45 billion in revenue by mid-2016, the dim prospect for continued revenue *growth* from a

²¹⁰ In summing up her interviews with a group of health economists, the journalist Sarah Kliff (2014) wrote, "Sovaldi, many of them argued to me, is exactly the type of drug we should reward with high prices. Economists argue that there's a tension in setting the price for a breakthrough drug like Sovaldi. We want to encourage more pharmaceutical companies to pursue similarly big developments — a cure for Alzheimer's, for example, or diabetes — but also want patients to have access to those treatments. When push comes to shove though, many prefer that we err on the side of higher prices as a way to encourage other big, blockbuster drugs in the future." As a reminder, Sovaldi is the brand name for *sofosbuvir*.

curative therapy sank Gilead's share price by almost 50% from its peak in mid-2015 to its current trough in April of 2017 (Chen 2017; Crow 2016a; Nisen 2017).

To boost their share price in the context of a curative therapy, Gilead turned to a three-fold strategy: a large-scale marketing campaign for hepatitis C, the accumulation of capital for potential acquisitions as well as distributions of capital to shareholders through buybacks, and a shift in attention to their 'chronic franchise' (HIV medicines) which can be used in a growing number of patients for a long-time horizon. Under the conditions of shareholder-driven financial growth, a curative therapy for a chronic disease pushed Gilead *towards incremental advances for life-long HIV treatments* rather than reinvestments towards breakthrough innovations (i.e. a cure for HIV).

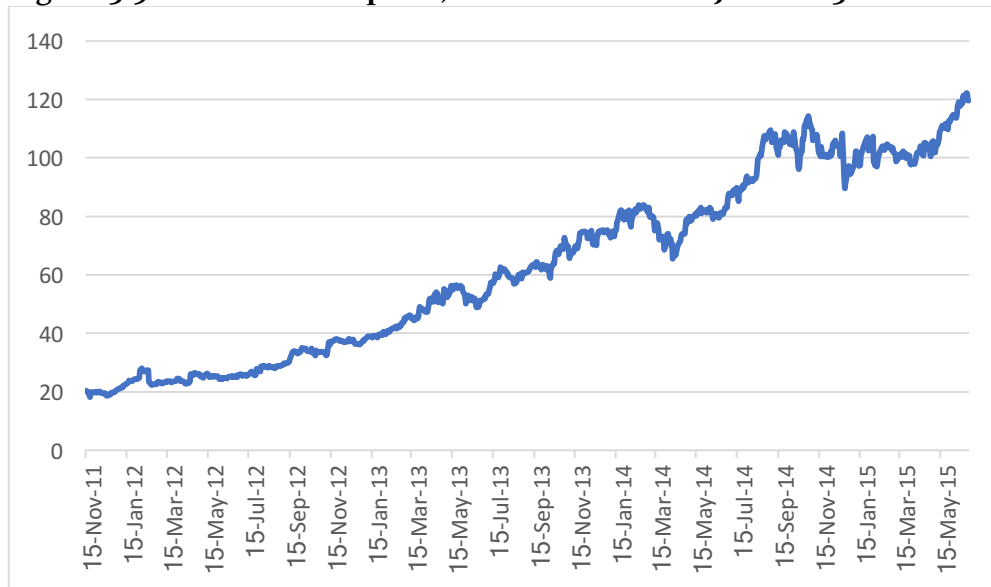
In this section, I draw on Gilead's financial statements, historical share prices, media accounts, and transcripts of earnings call between investment analysts and senior leadership to trace the response of financial markets to Gilead and the company's strategy in the three years since the launch of *sofosbuvir*. I begin by describing how shareholders initially valued Gilead with the surge of hepatitis C revenues in the two years after the launch of *sofosbuvir*-based medicines followed by their subsequent concern with diminishing prospects for growth. I then turn to the three-fold strategy Gilead attempted to employ in the face of those concerns.

5.3.1 An initial honeymoon for Gilead

Gilead experienced success by every financial metric in the months after their launch of *sofosbuvir*-based medicines. As highlighted in chapter 4 (and captured in Figure 5.8 below), Gilead's revenues tripled in two years, going from an \$11 billion a year company in sales in 2013 to over \$30 billion in 2015, mostly on the strength of their hepatitis C medicines (Gilead Sciences 2017). In 2015, these medicines alone made up \$19 billion of their total sales, with HIV medicines accounting for most of the rest (Gilead Sciences 2017). Investment analysts viewed Gilead's hepatitis C launch in historic terms. In their 2014 first quarter call, one of biotech's leading investors, Mark Schoenebaum, congratulated Gilead's senior leadership on the "best launch of any drug of all time, that I'm aware of at least," with a fellow analyst, Brian Skorney adding, "let me congratulate you and maybe even one-up Schoenebaum by saying I think this was actually the biggest single quarter for a pharmaceutical product in U.S. history" (S&P Capital IQ 2014). Wall Street valorization translated into major gains for Gilead's shareholders, as they anticipated near-term revenue growth in each subsequent quarter.

When Gilead bought Pharmasset in late November, 2011, their share price stood at \$19/share. By June of 2015, Gilead's price had leapt to \$122 per share. Figure 5.7 captures the rise during this period, with the price increasing during 2012 and 2013 largely on the strength of the *anticipated* approval of sofosbuvir in late 2013, with actual sales and revenue growth driving the rise in 2014 and 2015. As highlighted in the prior chapter, Gilead's senior executives, as significant shareholders themselves, were major winners from this share price escalation. This honeymoon, however, would be short-lived.

Figure 5.9 Gilead's share price, November 2011 to June 2015

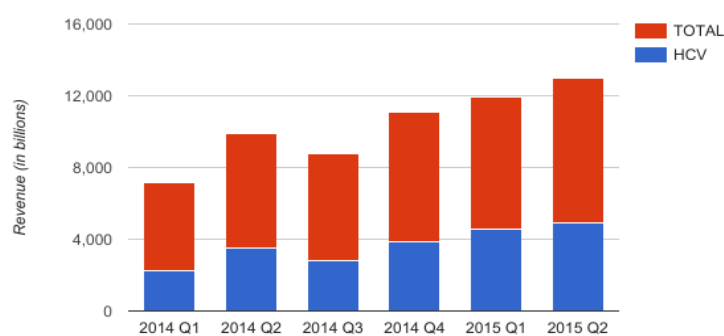


November 2011: \$19/share

June 2015: \$122/share

Source: Google Finance (GILD)

Figure 5.10 Gilead's hepatitis C (HCV) sales drive quarterly revenue growth



Source: Gilead's SEC filings

5.3.2 A patient cliff for hepatitis C

Sofosbuvir-based treatments laid bare a clash between public health and the conditions of shareholder-driven growth: while providing universal treatment via a cure to reduce an infectious disease and end an epidemic would be the best public health outcome, a cure also meant that a finite number of patients would become smaller and smaller over time. In other words, *sofosbuvir* would lead not to a ‘patent cliff’, but a *patient cliff*: the elimination not only of a disease over time, but Gilead’s ‘market’ of patients for continued growth.

This concern was demonstrated in Gilead’s conversations with Wall Street analysts from the time of their Pharmasset acquisition in 2011 and onwards from their launch in late 2013. On a call to announce Gilead’s acquisition of Pharmasset, Thomas Wei of Jeffries investment house inquired about the epidemiological modeling that allowed Gilead to arrive at an \$11 billion price for Pharmasset, with John Milligan, Gilead’s COO, offering a reassurance (S&P Capital IQ 2011a:14-15):

Thomas Wei (Jeffries): “When you modeled the market to get this valuation, how did you deal with the shape of the sales curve here? Did you take the approach that there would be a bonus initially with big sales and then falling to steady-state like what you’ve said about prevalence and incidence? Or did you assume that sales could grow continuously over time?”

John Milligan (COO, Gilead): “So many markets, *certainly chronic markets, continue to grow over time. And this (hepatitis C) does have a different-shaped curve*, but we see the curve being not as sharp as many have predicted, more flat and proceeding at a very high level of sales well into the late 2020s.”

In this exchange, Milligan surmised that because of its limited growth potential, a curative therapy possessed limitations as opposed to one for a ‘chronic market’; yet he also reassured Wall Street that high sales would continue for the life of their patent protections over *sofosbuvir*-based treatments.

When publicly financed health systems like the U.S. Medicaid program restricted access to the treatment later in 2014, investors openly wondered about the promise of triage for Gilead’s long-term growth potential. Michael Yee (2014:1), a leading investment analyst for the Canadian investment bank RBC Capital Markets, summed up this possibility in a note to his clients in May 2014:

“If payers prioritize or ration patients and limit use to only F3-4—would this be bad

because F3-4 is only 30% of the market? Our conversations with investors over the last week is peak revenues might be less near-term but long-term tail is much longer...so this is much more attractive...*so if anyone including Medicaid starts to limit to only sicker patients, this wouldn't dramatically worry us and could be better long-term.*"

Though treating patients in earlier stages over liver scarring (Fo-F2 levels of fibrosis in the most common staging system) can reduce risks of disease progression and transmission, Medicaid restrictions could in turn lead to the disease spreading to a higher number of patients than a scenario of universal treatment (Canary et al. 2015). In the view of Yee and his fellow investment analysts, the "long-term tail" of revenues could prove much longer, and higher.

As Gilead looked forward, the company estimated ~4 million people infected with hepatitis C in the US, with less than a 1/3rd of those diagnosed or treated (S&P Capital IQ 2014). This meant that growth would be driven by a steady flow of undiagnosed patients getting tested and diagnosed, and then diagnosed patients then getting treated. More than a year into Gilead's launch, however, investment analysts wondered about the company's projections on a February 2015 earnings call (S&P Capital IQ 2015). Cory Kasimov of JP Morgan asked Gilead's senior leadership, "Try to give us a little bit more comfort on how we can be thinking about this longer-term evolution in the U.S.?" John Milligan, Gilead's COO at the time, comforted, "our most recent data still suggests there's about 1.5 million patients diagnosed in America, which means that – and that was about 1.6 million when we launched (*sofosbuvir*). So that implies that there has been a refilling of that bucket, a replenishment, if you will." By identifying the large number of patients still working through 'buckets' of undiagnosed to treated, Milligan aimed to demonstrate the available growth potential for Gilead's hepatitis C medicines.

Yet analysts on Wall Street had run their own epidemiological models of hepatitis C under different pricing, treatment, and competition scenarios. Figure 6.9 shows Bloomberg financial analysts' prediction of three hepatitis C 'market scenarios' for Gilead (Nisen 2016). The scenarios shared one trend in common: a downward revenue trajectory. Gilead's predicament came in part from the population level dynamics of hepatitis C that had been triggered by the launch of *sofosbuvir*-based medicines. Before 2013, a sizeable proportion of patients had delayed treatment for many years due to the toxicity and lower response rates of prior interferon-based therapies (Alberti et al. 2014).²¹¹ With Gilead's treatment approved in late 2013, these patients-in-waiting

²¹¹ This phenomenon in which physicians recommended delayed treatment for their patients with hepatitis C in order to use better therapies that are anticipated to be approved in the near future is known as

turned up at higher numbers than the company originally estimated (United States Senate, Committee on Finance 2015). The large numbers of sick patients eligible for treatment - even under restricted access guidelines - combined with the company's launch pricing fueled a surge of revenue growth in 2014 and 2015. Yet the velocity of this growth appeared to be impossible to sustain with a curative therapy, and the Bloomberg sales curves - which also included consensus predictions from across Wall Street - captured this likelihood.

By 2016, Gilead's own sales reports and forward guidance from the company's senior leadership to investment analysts began to confirm this forecast. With Gilead's hepatitis C sales starting to plateau, analysts focused on the limitations of the company's growth potential with these curative medicines (Crow 2015; Nisen 2017; Silverman 2016a). When Gilead 'disappointed' Wall Street analysts with second quarter sales in 2016 of \$7.7 billion - viewed by financial markets as a 19% decline in sales compared to the same quarter in 2015 - the company's share price fell by nearly 10% (Stynes 2016). Deutsche Bank analyst Gregg Gilbert noted, "while management pointed to increasing screening volumes and confirmed its prior estimate of about 1.5 million people in the US who are yet to be diagnosed, it also anticipates a gradual decline in new patient-starts going forward, especially in mature markets such as the US, Germany, and France." These gloomy predictions, now shared by both Wall Street analysts and Gilead's senior leadership, led to a progressive decline in Gilead's share price (see Figure 5.10): from its peak of 122 per share in June of 2015, the price fell below ~70 per share by late January of 2017. A trader Bret Jansen (2016) summed up Wall Street's view of Gilead in late 2016:

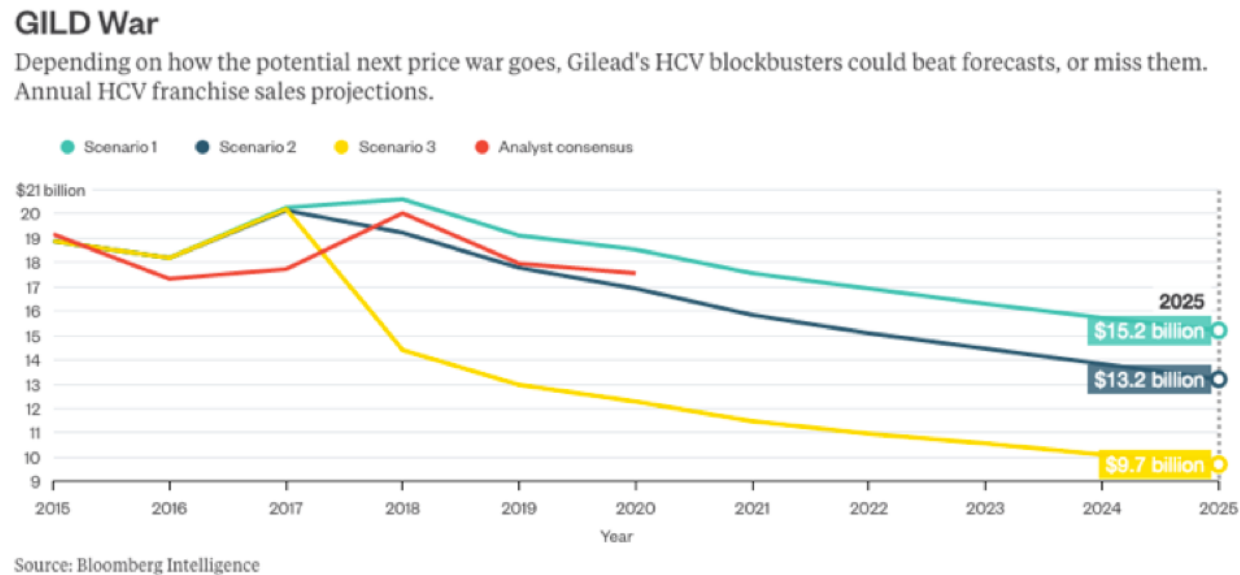
"Being a shareholder in biotech juggernaut Gilead Sciences over the past two years has been akin to being stuck in the classic 'Waiting for Godot' as one feels like he is waiting for some thing that will never happen. Despite seeing a ~600% increase in earnings from FY2013 through FY2015 driven by the blockbuster success of hepatitis C cures Sovaldi and Harvoni, the stock has gone nowhere as investors have worried that hepatitis C sales will continue to decline in the United States as the sickest patients have been treated and new competition will continue to emerge in this lucrative space."

Gilead's rate of profitability - 55% in 2015 and 45% in 2016 - became insignificant under this calculus of shareholder-driven growth (Gilead Sciences 2017). Even with over \$45 billion in revenue from hepatitis C sales, the diminishing prospects for near-term growth created a predicament for Gilead and its senior leadership. This predicament and Gilead's response to it

'warehousing' (Alberti et al. 2014). Once the warehouses were unlocked with the approval of *sofosbuvir*, Gilead experienced unprecedented growth which it could not sustain.

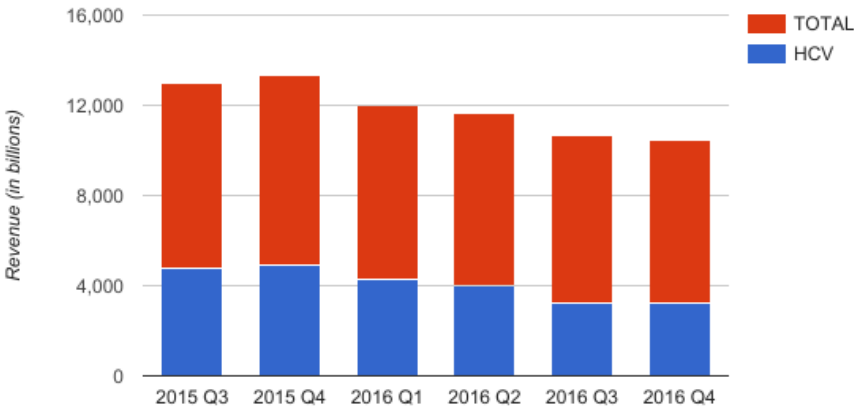
demonstrate the mechanisms underpinning the reproduction of financialisation and their consequences for innovation.

Figure 5.11 Bloomberg analyst forecast of Gilead’s hepatitis C revenue, 2015-2025



Caption: Each forecast by Bloomberg showed a steady decline in sales. Of note, the figure under the *lowest* forecast (scenario 3), still shows a sales figure of \$9.7 billion. But the *direction* of the sales trend, in this case showing the loss of revenue, pushed Gilead’s share price downward. See Figure 5.14
Source: Nisen (2016)

Figure 5.12 Gilead’s hepatitis C sales plateau and decline, 2015Q3 – 2016Q4



Source: Gilead’s 10-Q filings

Figure 5.13 Gilead's share price, June 2015 to May 2017



June 25, 2015: \$122 per share

May 9, 2017: \$67 per share

Source: Google Finances (GILD)

5.3.3 Generating growth for shareholders: advertising campaigns, cycles of acquisitions and buybacks, and chronic therapies

The shareholder-driven pressures for short-term growth created glaring questions for Gilead. In a January 2016 Financial Times piece titled, “Gilead risks becoming victim of its own success,” the company’s executive vice president Paul Carter worried, “There’s this sort of pressure now we are a \$30 billion a year revenue company. People are asking where the next 8 or 10 percent of year on year growth is going to come from” (Crow 2016a). In other words, the greater the magnitude of growth for the company in the recent past, the larger the growth would need to be in the near future.²¹²

Gilead’s response demonstrates the ways in which the innovation process is configured by the relations of power between shareholders and business. I traced Gilead’s response to this pressure by drawing on media accounts, transcripts containing the statements of Gilead’s senior leadership such as earnings call meetings, and Gilead’s financial statements.

²¹² Carter’s concern reflects their basic arithmetic challenge: generating 8-10% growth on \$30 billion revenue would push up the absolute amount (\$2.4 billion to \$3.0 billion) by which Gilead had to grow to meet expectations versus when it was a \$10 billion dollar revenue company (\$800 million to \$1 billion in growth would suffice).

The evidence from these sources of data indicate that Gilead attempted to deploy three strategies (see Table 6.3): (1) maximizing its hepatitis C sales via a major marketing campaign, (2) a financial cycle of acquisitions, buybacks, and price increases²¹³, and (3) a shifting focus towards developing its chronic therapy business (HIV/AIDS). These strategies all aimed at generating growth within a time frame that would increase their share price in the near-term.

Table 5.3 Three strategies to generate growth in revenues and share price

Strategy	Execution of strategy	Examples from Gilead
Boost sales of existing products	<ul style="list-style-type: none"> - Increase marketing and geographic reach - Increase prices of current medicines 	<ul style="list-style-type: none"> - >\$100 million advertising campaign for hepatitis C to boost number of patients who are getting tested and treated early in the disease process - Price increases on HIV drugs
Financial market maneuvers for acquisitions and buybacks	<ul style="list-style-type: none"> - Stock pile cash and debt to capitalize on late-stage drug assets via the financial market - Use share buybacks and price increases to generate boost for share price, which can be used as leverage to raise debt for acquisitions or pay for further buybacks 	<ul style="list-style-type: none"> - Over \$20 billion in cash stockpiled from sales - Price increases on HIV drugs - \$15 billion of debt issued on open market - Gilead viewed in financial markets as likely 'buyer' in near future
Chronic therapy clinical trials	<ul style="list-style-type: none"> - Focus on late stage clinical trials for medicines that will require long-term patient use and extend patent protection for long time horizon 	<ul style="list-style-type: none"> - Late-stage clinical trials on already-developed compound for HIV that will create new patent rights for Gilead into late 2030s in a 'market' that can continue to grow (unlike hepatitis C)

Marketing campaign to maximize hepatitis C sales

One of Gilead's strategies to boost growth involved getting more people in the US infected with hepatitis C to visit their doctors, get tested, and eventually use the *sofosbuvir*-based treatment.²¹⁴ Because hepatitis C is a chronic disease that unfolds over a long period of time, many people are either unaware of their infection or the fact that new curative medicines are now available without the toxicities that might have discouraged them from seeking treatment in the past (Harris 2009; Rhodes et al. 2013; Rosen 2011a). From Gilead's view, this meant lost revenue and a chance to boost sales growth in the near-term by driving more patients to visit their doctors. Though a marketing campaign held the potential for providing a public health service by

²¹³ I return to buybacks here in order to situate them as part of Gilead's overall capital allocation and business strategies as well as their ineffectiveness (and value destroying consequences) in counteracting the financial market reaction to a curative therapy.

²¹⁴ US government policy allows for direct to consumer marketing of medicines.

raising awareness on the disease, Gilead's strategy – drawn from a STAT Health investigation as well as the US Senate Finance committee report – exacerbated the uneven deployment of the medicine.

Gilead developed their marketing approach to target those populations most likely to either have private health insurance through employment or Medicare (the health insurance system in the US for people over the age of 65), which as I highlighted in section 5.2, cannot negotiate drug pricing or restrict access (Robins 2016; United States Senate, Committee on Finance 2015). Their aim was to remind people, typically at the earlier stages of disease, about the potential seriousness of hepatitis C (see Figure 5.15). To deploy this message, Gilead spent more than \$100 million on a multi-pronged marketing campaign for hepatitis C between the spring of 2015 and 2016, and which continues to run in 2017 (Robins 2016). According to a STAT Health investigation that analyzed Gilead's marketing campaign, the company ran more than 11,000 ads for their *sofosbuvir*-based regimens aired on multiple TV channels, from FOX to the Game Show Network. According to media research firms iSpot.tv and Kantar Media, Gilead's spots during that time cost an estimated \$60 to \$80 million (Robins 2016). Alongside the TV ads, Gilead bought more than \$30 million in magazine ads from People to Popular Mechanics, as well as \$5 million in online ads (Robins 2016).

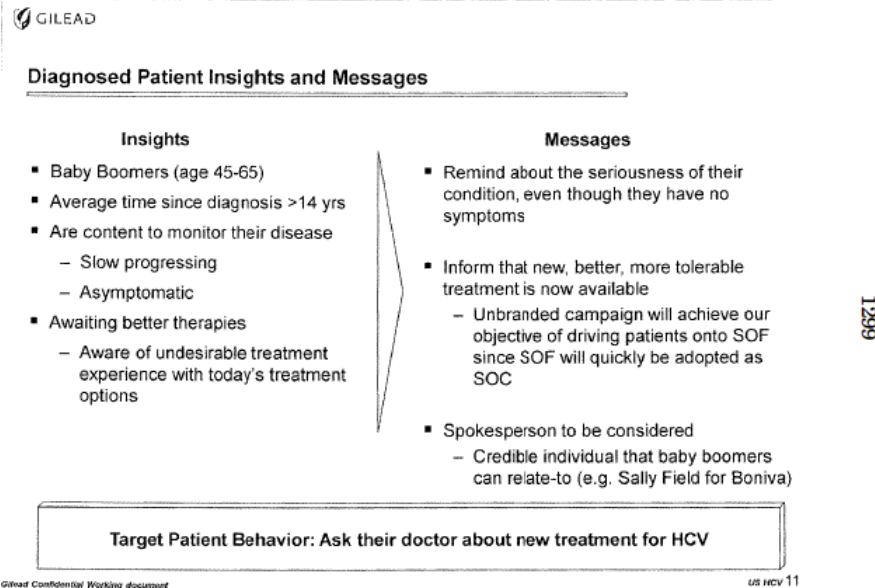
Their leading advertisement as part of the campaign, titled "Hepatitis C and Baby Boomers" shows greying men and women in the foreground with statistics of a 'forgotten virus' in the backdrop. The ad aims to get all Baby Boomers²¹⁵ tested for hepatitis C (by sharing that '1 in 30 Baby Boomers have hepatitis C') and that those are diagnosed be cured using their treatments. The money and strategy delivered on Gilead's intended marketing outcome (see Figure 5.15) – "ask their doctor about new treatment for HCV" (United States Senate, Committee on Finance 2015:1299). As part of an interview to STAT Health, a leading hepatologist, Dr. Douglas Dieterich of Mt Sinai, explained, "patients have Harvoni on the mind because of these TV commercials," adding, "we're battling their successful direct-to-consumer advertising" (Robins 2016). In order to sustain and expand their position in the innovation process – as an acquisition specialist capable of continuous growth – Gilead translated their accumulation of capital into marketing influence. Notably, this marketing influence was aimed at the most lucrative market – older patients with

²¹⁵ Baby Boomers refers to the demographic group born in the US during the post-World War II era between the years 1946 and 1964. The term is culturally typically linked to the wealth and privilege of the generation, growing up in the post-War boom.

private insurance or Medicare. Gilead’s marketing approach to Baby Boomer populations, however, contrasted sharply with the rationing approach employed in Medicaid and the US prison system – the populations precisely most at-risk for untreated disease progression and transmission (Beckman et al. 2016; Loftus and Fields 2016).²¹⁶

Though Gilead’s marketing enabled the company to continue to generate higher sales for hepatitis C than otherwise would have been possible, their efforts in hepatitis C alone would not provide the magnitude of growth necessary to meet the expectations of shareholders. Addressing this challenge would require an entirely new source of revenue.

Figure 5.14 Gilead marketing aimed at Baby Boomer patients



Caption: Internal Gilead document depicting their marketing strategy and aims for sofosbuvir-based treatments. Their focus was to remind Baby Boomer populations “about the seriousness of their condition, even though they have no symptoms”.

Source: United States Senate, Committee on Finance (United States Senate, Committee on Finance 2015)

A focus on acquisitions and buybacks

Though the marketing campaign aimed to boost Gilead’s hepatitis C sales, the overall trajectory of growth – the 8-10% expectation noted earlier by Paul Carter, Gilead’s Executive Vice President – would require a new product and its associated stream of revenues. Phil Nadeau, an investment analyst at Cowen, summed up Gilead’s dilemma:

²¹⁶ Gilead noted in a 2013 market strategy that the Departments of Corrections “may not be a Gilead target” (United States Senate, Committee on Finance 2015:1265), and subsequently did not pursue any contracts with prison systems; care in US correctional system is largely on an ad-hoc basis (Loftus and Fields 2016).

“We suspect that for Gilead’s stock to become a top performer, management must change the conversation among investors from ‘how quickly will hepatitis C decline, and how soon?’ to ‘How much can product X grow Gilead’s revenue?’ Such a turnaround of sentiment is difficult for any biopharmaceutical company, and *even more so for one with \$30 billion in product sales*” (Silverman 2016a).

Not only would Gilead need a new product, but one that could deliver significant growth on top of Gilead’s recent escalation. One obvious possibility for finding a ‘product X’ could have been in plain sight: Gilead’s own innovation pipeline.

Yet Gilead’s internal pipeline lacked value in the eyes of Wall Street²¹⁷, with Brian Skorney of RW Baird seeing “few opportunities for such growth in the company’s existing pipeline as is” in a note after Gilead’s earnings call in early February 2016 (Silverman 2016a). Piper Jaffray’s Joshua Schimmer went further, expressing his frustration that Gilead “has not impressed us with its development capabilities beyond HIV and hepatitis C”. He went on, “we have little enthusiasm for most of what we consider to be a highly speculative pipeline and nowhere close to the level we would expect from such an important and sizeable company...There is not a single program which we even find worth highlighting (Silverman 2016a).”²¹⁸ As described in chapter 5, Gilead’s investments in research and development had paled in comparison to its revenues, and their internal pipeline reflected this under-investment. Growth, in other words, appeared less likely to come from Gilead’s own research and development. Gilead would instead turn towards a familiar financial cycle translating its position as an accumulation center in the innovation process to pursue potential acquisitions while also directing capital to shareholders via buybacks and dividends.²¹⁹

Acquisitions remained Gilead’s as well as Wall Street’s favored vehicle for achieving new revenue growth to sustain this financial cycle. When the Financial Times caught up for an interview with Norbert Bischofberger the company’s head *research and development official* in

²¹⁷ I drew these investor notes from a report in STAT Health, see Silverman (2016a), which corroborated my reading of earnings call transcripts, reports from other investment analysts, and other media accounts.

²¹⁸ This evaluation may be a product of investment analysts’ difficulty in valuing any early-stage compounds, thereby pushing companies to focus on late-stage compounds and acquisitions (and thereby creating a self-fulfilling process, with dry pipelines). In Birch’s (2016) interviews with biotechnology executives, one executive shares this possibility: “The focus has shifted more towards how close are we to profitability? So it’s sustainable profits is like a key focus rather than delivering value from the pipeline because investors don’t value sort of R&D projects that are pre-phase three essentially. And so it’s all about kind of keeping costs under control, maximizing the revenue we can generate from our lead assets, acquiring companies that have got royalty streams that bring in royalties on drugs that have already been launched.”

²¹⁹ I detailed Gilead’s focus on acquisitions and buybacks in a letter to the BMJ written with Dr. Lawrence King. See Roy and King (2016).

December of 2015, he did not focus on the company's internal research and development prospects, but rather the company's strategy towards acquisitions (Crow 2015). In a piece titled, "Cash rich Gilead hits the acquisition trail", Bischofberger recounts their approach to Pharmasset as an ideal model moving forward: "Philosophically, we prefer to wait for more certainty and pay more money, which is what we did with Pharmasset, rather than getting something cheap with uncertainty" (Crow 2015). This acquisition strategy required capital, which Gilead would draw from two sources: cash and debt.

When asked what the company was going to "do with all its money", Bischofberger continued, "Well, we have our eye on the external world—we have incredible cash flows and we are looking for opportunities" (Crow 2015). Indeed, Gilead had accumulated over \$20 billion in cash by early 2016 (it had \$32.4 billion by the end of 2016), much of it on the winds of hepatitis C sales (Crow 2015; Nisen 2017).²²⁰ In order to finance an acquisition, however, Gilead also raised debt – not from banks, but through selling 'corporate notes' (essentially IOUs) on the open market (Glabau 2016a; Roy, Hawksbee, and King 2016b).²²¹ This debt would enable the company flexibility to direct capital towards a potential large-scale acquisition or further share buybacks. Gilead had used this strategy previously with its acquisition of Pharmasset in 2011, which relied on leveraging its significant cash from HIV sales – which had in turn depended on annualized price increases.²²² Annualized price increases in the US market, a common practice by pharmaceutical companies, thus are a lever not only for generating growth, but also with using the accumulated cash (and potentially increasing share price) as leverage in raising debt capital for buybacks and

²²⁰ As of their Q3 2016 financial statement, Gilead had \$25.2 billion of their cash in accounts outside the United States in order to avoid paying US corporate tax (Nisen 2017).

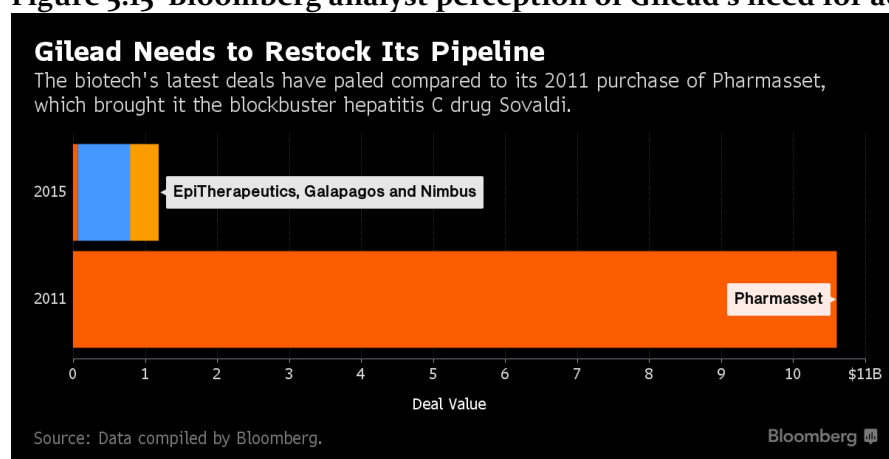
²²¹ Though Gilead did not have to use any of its assets as collateral in order to borrow through the issuance of what are called 'unsecured senior notes', it's 'A' credit rating by rating agency Moody's – due to its past performance, debt payments, and stockpiles of cash – allowed them to issue these notes at favorable interest rates (~3%). Raising debt by going directly to lenders through corporate note issuances, rather than through banks for loans, is an example of the kind of financial dis-intermediation (removing banks as mediators between lending and borrowing) that is explored in other works, such as Krippner's work on financialization (Krippner 2005; 2011). I point to this dynamic here to show the ways in which Gilead's capital allocation strategy aimed less at tangible investments in research but rather financial maneuvers aimed at buttressing their position for potential acquisitions and buybacks.

²²² Between 2006 and 2011, Gilead had increased the prices of its HIV medicines from \$13,800 per year to \$25,874 per year (Fair Pricing Coalition 2015). Gilead continued this practice over this period and into 2016, when it raised the price of its hypertension drug Letairis and its HIV regimens Complera and Stribld by 7 percent each in July 2016, coming off 5 and 7 percent increases on those two drugs in January of 2016 (Silverman 2016c). The prices of Gilead's HIV regimens now exceed \$30,000 per year. Combined with free cash flows from hepatitis C revenue, this revenue was used to pay for buybacks and stockpiled for a potential acquisition.

acquisitions (Glabau 2016a; Roy, Hawksbee, and King 2016b). Between 2015 and 2016, Gilead followed the strategy they had used prior to Pharmasset, leveraging their accumulated cash to raise \$15 billion in debt on the open markets (Palmer 2016; Terry 2015).

These moves positioned Gilead for a major acquisition. Leading biotechnology analyst Mark Schoenbaum probed Gilead's senior leadership in an earnings call (Seeking Alpha 2016a): "The biggest question on everyone's mind for Gilead is, "Who are you going to buy? Who are you going to buy? Who are you going to buy? Who are you going to buy?" Every day this is what we talk about in investment circles." Since Gilead's acquisition of Pharmasset, the company has not made a 'transformative deal' on that scale. A series of smaller acquisitions had yet to yield a product with major growth potential, with Figure 5.16 from a Bloomberg piece representing the financial sector's dim view of Gilead (Chen 2016). Though the company's senior leadership continued to scan the market of pharmaceutical assets into 2017 to find their next Pharmasset, they would not have an answer for Schoenbaum.²²³

Figure 5.15 Bloomberg analyst perception of Gilead's need for acquisitions



Caption: The title of the slide sums up traders' preferred strategy for Gilead to generate growth via its pipeline: re-stock it by looking outside the company. Source: Chen (2016)

While speculation about Gilead's acquisition possibilities continues at the time of my submission, Gilead's senior leadership pointed investors towards the other component of their financial strategy: directing capital towards shareholders. Bischofberger shared the company's thinking on an earnings call in 2016:

²²³ Some industry and investment analysts wondered whether the company needed a change in management, or even could get bought out by a larger competitor due to its falling market capitalization (Budwell 2016; Williams 2016).

“If you look back at the last six years, it has been remarkable. *We have done many, many deals* – CGI, Arresto, Calistoga, Pharmasset, Galapagos²²⁴ – and yet, *we were able to return 70% out of free cash flow to shareholders*. So I think that is a good way to think about the future, to in-license through collaborative efforts while at the same time *returning money to shareholders*” (Seeking Alpha 2016a).

Indeed, as I documented in the prior chapter, Gilead announced a series of major share buybacks with their new hepatitis C revenue. In just the first six months of 2016, for example, Gilead bought back \$9 billion in its own shares, about three times their entire research and development budget for the year (Gilead Sciences 2017). Robin Washington, Gilead’s Chief Financial Officer, communicated the company’s rationale:

“*We have purposely focused on share repurchases because in the absence of M&A it allows us to be flexible and more opportunistic*. But when the right M&A opportunities present themselves, it allows us to reduce our share repurchases in order to make those *necessary acquisitions and leverage our cash and debt and borrowing if we need to*” (Seeking Alpha 2016b).

Washington here focuses on buybacks as a form of *flexibility* in Gilead’s strategy towards shareholders; where dividends create expectations among shareholders for a return at regular intervals, buybacks aimed to boost Gilead’s share price in the near term while also keeping capital – cash and debt – available for a future acquisition.

But as I have chronicled in this chapter, Gilead’s share price has fallen *despite* this significant share buyback program; the failure to generate near-term growth with a curative therapy led the company to lose \$41 billion in market capitalization between mid-2015 and end of 2016 – which buybacks, with their transient, short-term effects could do little to affect (Budwell 2016). As Table 5.4 below shows, Gilead used \$23 billion in capital – a mix of its cash and debt – to purchase its own shares. Yet as the average share prices indicate, the buybacks had little effect in redressing their decline. Seen with this context, the share buyback program *destroyed value* – both by limiting reinvestments back into research and development and also failing even to boost the

²²⁴ CGI, Arresto, Calistoga, and Galapagos all were smaller acquisitions by Gilead (Rangan and Lee 2009).

company's share price for its shareholders (Nisen 2017).²²⁵

Table 5.4 Gilead's share buybacks and average share price after *sofosbuvir* launch

Share buyback program (by month of announcement)	Total dollar amount of shares purchased	Average purchase price
May 2014 program	\$5 billion	\$102.36
January 2015 program	\$10 billion	\$100.85
January Q1/Q2 accelerated program	\$5 billion	\$92.09
January 2016 program	\$3 billion	\$84.11
TOTAL AMOUNT	\$23 billion	

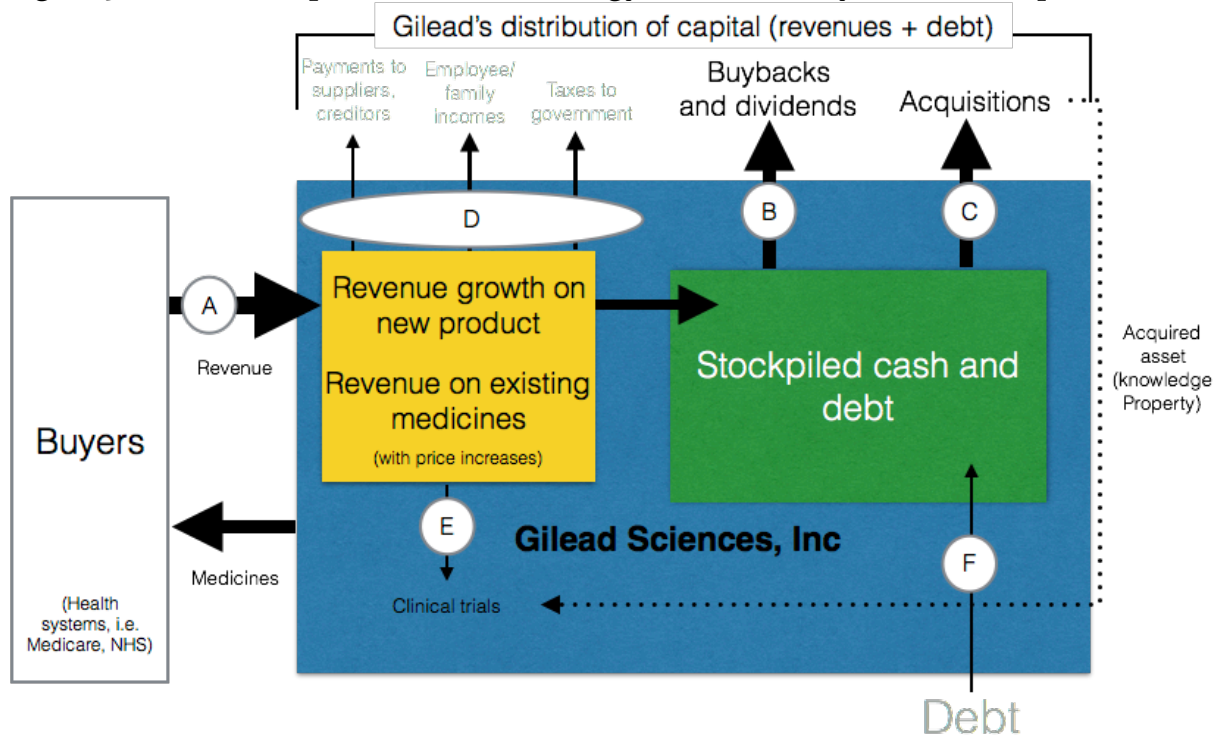
Caption: Companies typically announce a share buyback program with a given amount and then report the average purchase price of the actual shares later purchased through that program. Here, Gilead's share price fell even as they bought back billions in their own stock.

Source: Gilead's 2016Q4 earnings slides

In sum, these strategies formed a kind of 'financial toolkit' (see Figure 5.17), via which the company aimed to leverage cash and debt towards an acquisition while also directing the majority of its capital towards buybacks and dividends in the attempt to 'increase shareholder value' (see Figure 5.17 for a visual flowchart of this strategy). John Milligan, now the CEO, synthesized the toolkit on an earnings call, "For us it's fairly simple. We have the flexibility to do both things; that is, return shareholder value through stock repurchases and dividends and of course continue to be opportunistic in M&A" (Seeking Alpha 2016c). In attempting to generate growth for shareholders, reinvestments within the business thus remained at the margins of their capital allocation strategy.

²²⁵ A Bloomberg reporter Max Nisen (2017) described this buyback strategy as a "more efficient way to destroy value than an acquisition, with none of the upside", in a piece entitled, "Gilead Mismanaged its Gold Mine".

Figure 5.16 Gilead's capital allocation strategy: a focus on buybacks and acquisitions



Caption: This diagram follows Gilead's capital allocation strategy, which focuses on using revenue from health systems (A) combined with leveraged debt (F) for buybacks and dividends (B) and acquisitions (C), with a fraction going towards clinical trials (E - often on acquired late stage assets, like Pharmasset's PSI-7977) and payments (D) to workers, contractors, and government.

A shifting focus from curative to chronic 'innovation'

As Gilead directed returns to shareholders and waited for potential acquisitions, they also turned to a focus on ways to generate growth within the company that could begin in the near-term and also sustain into the long-term. Investment analysts too wondered how Gilead could deliver this growth. An exchange at Morgan Stanley's annual health care conference in September of 2016 between an analyst and Gilead's CEO, John Milligan, reveals Gilead's approach (Seeking Alpha 2016c):

Matthew Harrison (Morgan Stanley): "It feels like the default investor view point is that Gilead has to be a growth company. So do you think that's reasonable, do you think that's accurate?"

John Milligan (CEO, Gilead): "We (Gilead) had an unprecedented rate of growth through 2015, essentially tripling revenue in three years. *That's a very challenging thing to grow off of. [...]* So that (hepatitis C) doesn't lead to the continuous growth that you would want. Still great economically, still great in cash flow and will be a very important product category for us for the next decade or beyond.

But I separated (hepatitis C and HIV) at the beginning for a reason. *If you look at where we can focus and what we can do, it's really off that base HIV business. I think what'd like to see is that business continue to grow and really ultimately eclipse the HCV business through new products and growth out of our pipeline, which we certainly have the potential to do in the coming decade.*"

In this response, Milligan outlined Gilead's predicament of near-term shareholder-driven growth, and the resulting direction for the company with regards to future innovation. As Milligan reminded us, the growth predicament is two-fold. First, *growing off growth* is itself a challenge. Second, a curative therapy "doesn't lead to the continuous growth that you would want". Both the magnitude and velocity of growth expected by shareholders posed a threat to Gilead. To address this threat, Milligan shifted the attention of the audience to where Gilead had placed its near-term hopes: "if you look at where we can focus and what we can do, it's really *off that base HIV business*". Why is this the case? As I documented in the prior chapter, Gilead's HIV medicines are not a curative therapy; rather, patients with HIV must take them as a lifelong treatment. This allows these assets to not only endure through out the entire course of Gilead's intellectual property rights, but also can be used in a growing number of patients, as the main 'loss' is not due to cure but due to an eventual death.²²⁶ This financial imperative shaped Gilead's approach to innovation with the company – *rather than use the money for hepatitis C internally to pursue a curative treatment for HIV, Gilead maneuvered to make incremental improvements in HIV medicines by extending patent protection over a potential 'growth market asset'*.

Gilead's intellectual property protection for one of their two backbone HIV compounds, *tenofovir disoproxil fumarate* (TDF), was set to expire in 2017 (Gilead Sciences 2012). This would expose their two main HIV/AIDS regimens, Complera and Stribild, to generic competition, since both contained TDF. This patent expiry threatened approximately \$11 billion in revenue (Gilead Sciences 2012). To counter this expiration, Gilead pursued approval of a "new" HIV compound with incremental but clinically significant improvements, *tenofovir alafenemide fumarate* (TAF) (Petersen 2016a). While the original TDF therapies were accompanied by significant side effects such as kidney dysfunction and bone loss in some patient populations, the new TAF therapies

²²⁶ This focus on HIV returns Gilead in some ways to its pre-2011, pre-Pharmasset acquisition period, in which growth from HIV had stagnated and had produced an earlier period of crisis. The difference now is that the company hopes that with new combinations, HIV regimens can produce steady growth (Silverman 2016a). Gilead's share price has continued to fall even with this strategy as shareholders and financial markets anticipate that this growth will fall short of the expected 8-10% clip, without a major acquisition or new product line.

showed reduced side effects with a smaller dosage based on a minor change in chemistry (Wang et al. 2016). This clinical improvement was used to justify approval in 2015 from the FDA (FDA 2015). Critically for Gilead's future growth, the intellectual property rights for their new HIV regimens (Odefsey and Genvoya, both containing TAF) will last well into the late 2020s and early 2030s (Petersen 2016a). For example, the compounds in Genvoya are protected by multiple patents, the last of which is set to expire in 2032. Odefsey is priced at \$2,346 and Genvoya is priced at \$2,578 per month in the US, amounting to approximately \$30,000 in annual costs for a medicine that is required over the remainder of a patient's life (Silverman 2016c). If a patient lives fifteen years (the length of the patent) on these medicines, Gilead will accrue \$450,000 per patient, and more if the company follows prior practices (described earlier in this section) and raises prices over time.

The story behind this "innovation" has drawn public scrutiny, serving as the center of a lawsuit in which patient groups have alleged that Gilead actually had the data on their new compound – TAF – over a decade ago, but deliberately delayed further clinical trials on TAF for several years in order to extend intellectual property protection for as long as possible (Petersen 2016b; Silverman 2016b). Legal filings show that Gilead scientists had, as early as 2001, published findings for a less toxic formulation of *tenofovir* than the TDF version, and even performed a small trial with 30 patients demonstrating this result in 2002 (Petersen 2016b). Yet the results for the small trial were not published until 2014, and Gilead's leadership halted further study on the compound until 2010 (Petersen 2016b). As trials were initiated with TAF after 2010 and accelerated in 2014-2016 (in part through their new hepatitis C revenues), Milligan reported to analysts that the new alternative could add "a great deal of longevity" to their HIV business, and replace the lost sales from patent expirations (Petersen 2016b). Figure 6.9 demonstrates the longevity and growth gained through the advent of their TAF-based therapies.

Thus, as Gilead accrued significant hepatitis C sales in 2014 and 2015, their internal organization was not directed at further innovation. Rather, Gilead's strategy with HIV demonstrates the dynamics of shareholder-dominated growth: rather than directing funding towards a curative therapy for a disease such as HIV/AIDS that affects millions of patients globally, Gilead instead focused on extending their hold over a 'chronic market', while continuing to distribute significant revenue to shareholders and stockpiling cash for a potential acquisition.

Table 5.5 Comparing TDF (old) vs. TAF (new), Gilead's backbone HIV compounds

Backbone compound	Key feature	Main Combinations	Patent expirations	Revenue implication
TDF (tenofovir diproxil fumurate) <i>Gilead's old backbone</i>	-Approved in 2001 by FDA - Significant improvements in HIV outcomes when used in combination, but leads to side effects (kidney dysfunction and bone loss).	Contained in Atripla and Truvada; also sold alone as Viread	- 2017 in EU for Atripla, Truvada, and Viread; 2021 in U.S. for Atripla and Truvada, 2018 for Viread	TOTAL sales in 2015 for TDF regimens: \$11 billion , accounting for 32% of all revenue
TAF (tenofovir alafenimide fumurate) <i>Gilead's new backbone</i>	-Approved in 2016 -Less dosage required leading to fewer side effects -Disputed clinical development; lawsuit alleges that Gilead held onto the compound since 2001 in order to use the TDF and TAF compounds sequentially to extend HIV market dominance	Contained in new Genvoya combination (main combination used) Also in Odefsey and Descovy	- 2032 in US for Genvoya - 2028 in EU for Genvoya	Just approved in 2016; expected to generate significant long-term revenue; see graph below

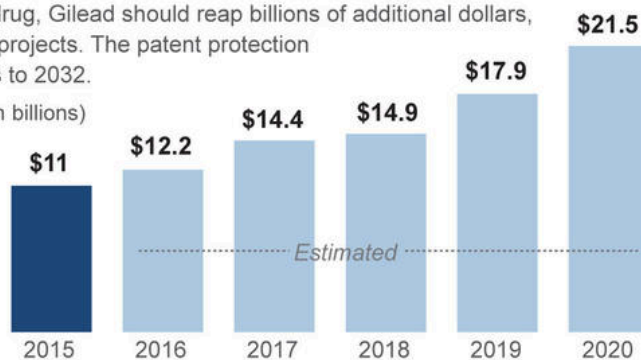
Source: Gilead's 10K filings

Figure 5.17 Gilead's expected growth from new HIV backbone

Extending HIV drug sales

With the introduction in November of a new, less toxic version of its key HIV drug, Gilead should reap billions of additional dollars, one analyst projects. The patent protection now extends to 2032.

Revenues (in billions)



Source: Geoffrey Porges, biotech analyst at Leerink Partners

Graphics reporting by Melody Petersen

Lorena Elebee / @latimesgraphics

Source: Petersen's (2016b) report in the LA Times

In this section, I chronicled the conundrum of a cure for realizing the growth that Gilead's shareholders expect. Sliding downward to a *patient cliff*, Gilead's share price declined in parallel between its peak of 122 per share in June of 2015 to less than 70 by May 2017. As Gilead's revenues from hepatitis C plateaued and began to decline *compared* to the year before, the company turned to a three-fold set of strategies to attempt to generate growth. First, I described Gilead's marketing campaign aimed at patients with private insurance or Medicare, the public program barred from negotiating prices or restricting access. Second, with no late-stage internal compounds promising new revenue, Gilead accumulated capital in the pursuit of an acquisition (along with leveraging debt) and distributed capital to shareholders through buybacks and dividends. Finally, I show how Gilead focused their attention on building their "base business" – therapies for HIV patients that would be required for a lifetime. Rather than directing revenue towards early-stage research for a HIV cure, the company performed late-stage clinical trials to extend their dominance over a "chronic market" which could deliver continuous growth.

5.4: Waiting on Value: a summary

In this final deployment phase of the innovation process, with an approved medicine ready to be priced and delivered across health systems, I illustrated the ways in which the mechanisms underpinning financialization shaped Gilead's pricing, the capability of state health systems to deliver optimal patient and public health outcomes, and finally Gilead's business strategy in the face of recurring crises of growth.

In the first part, I described Gilead's approach to pricing *sofosbuvir*-based treatments as a culmination of the *pricing escalator* which had in part fueled the mobilization of speculative capital behind Pharmasset, including Gilead's prior \$11.2 billion bet. The price of the existing standard of care at the time served as a reference 'base-line', with the company using surveys and interviews to estimate the upward limits of what health systems would be willing to pay for improved therapeutic outcomes. These considerations, along with evaluating the position of potential competitors, guided Gilead to a price of \$84,000 for their first wave of *sofosbuvir*-based regimens, and \$94,500 for their second wave.

This pricing dynamic created a crisis for the state, however, which I traced in the second part of the chapter. I showed that public health systems responded to the price by allocating significant budgets to treat only a small fraction of patients with hepatitis C, instituted access restrictions to contain costs, and deferred public health planning to eliminate the virus at a

population-level. The health delivery state, in this case, turned into a triage state, treating only the sickest patients to avoid the opportunity costs of health and social spending in other areas. Though Gilead's prices represented a 'value-based price' via conventional health economics measures of cost-effectiveness and averted downstream medical expense, I illustrated the pitfalls of these 'value' studies as well as the limited negotiating power of the state vis a vis Gilead with regards to drug pricing.

Finally, I observed how financial markets and Gilead's shareholders reacted to a curative market and thereby reinforced the extractive strategies employed in the innovation process. The dynamics of a cure market underlined the influence of financialization – even with annual rates of profitability exceeding 45% in the three years after the launch of *sofosbuvir*-based medicines, Gilead's market capitalization – as measured by its share price – fell in half by the beginning of 2017 from its peak in 2015. A curative therapy eliminated the very possibility of growth on which its value as an asset in financial markets depended. To transcend this shareholder-driven expectation of growth, the company directed its capital towards marketing campaigns, potential acquisitions and buybacks, and a focus on incremental advances for a chronic market.

With this account of the innovation process now complete, from the early stages of research beginning in the 1960s (chapter 3), onwards into the clinical development phase in the 2000s (chapter 4), into the deployment era of *sofosbuvir*-based medicines (2013-present), I now turn to synthesizing the key descriptive and evaluative claims in the dissertation that answer the two research questions I posed.

Chapter 6. Diagnosing Financialization in Sofosbuvir

Etiology, Outcomes, Justifications, Futures

To change the world, one has to change the ways of world-making, that is, the vision of the world and the practical operations by which groups are produced and reproduced.

- Pierre Bourdieu (1989: 23) in *Social Space and Symbolic Capital*

Over the past three chapters, I followed the organizational and political-economic dynamics in the innovation process behind *sofosbuvir*. This representation of the innovation process now provides the opportunity I take up in this chapter: to build an analytical synthesis that answers both research questions and can be used to understand the limits of the competing economic answers considered in chapter 1.²²⁷ In answering my first question, I argue that the prices of *sofosbuvir* did not represent the tangible costs of innovation or embodied health improvements for patients, but rather were a product of financialization: *a pattern of accumulation in which growth was pursued through the capitalization and control over intangible assets in financial markets*. In section 6.1, I dissect the etiology²²⁸ of financialization in the case of *sofosbuvir* by tracing the specific organizational relations of power and political-economic dynamics that can explain its price.

In answering my second evaluative question in section 6.2, I argue that *while entrepreneurial investment from the state shaped the direction of the innovation process towards a cure, the processes of financialization disconnected the distribution of risks and rewards, undermined the sustainability of the innovation process, and diminished patient and public health outcomes*. In answering both questions, I illustrated that the innovation process and its outcomes were a product of dynamic power relations at stake between multiple state, business, and financial actors in a politically and historically contingent context.

In section 6.3, I revisit the competing economic rationales of ‘risk’ and ‘value’ presented in chapter 1 and demonstrate their limitations in explaining *sofosbuvir*’s prices in light of the

²²⁷ As a reminder, I posed two research questions in chapter 1. My first research question aimed at a descriptive understanding: *how do the organizational and political-economy dynamics in an unfolding innovation process explain the pricing of sofosbuvir-based medicines for hepatitis C?* The second research question sought to evaluate the process and its distributive outcomes: *how were the risks and rewards of sofosbuvir’s development distributed across its innovation process, and what were the outcomes for the direction and sustainability of the innovation as well as for patients and public health?*

²²⁸ Oxford English Dictionary (2017) defines *etiology* as the cause, set of causes, or manner of causation of a disease or condition which is a subject of investigation.

evidence I have laid forth. I also illuminate the ways in which these claims are used in the innovation process as justifications of pricing that in turn aim to naturalize a given distribution of capital. A fourth section highlights the key contributions this dissertation makes and also identifies the limitations of the study, while translating each limitation into potential directions for future inquiry. I conclude with a brief post-script, reflecting on the broader questions and hopes that my investigation provoked.

6.1 The etiology of financialization in biomedical innovation and drug pricing

What follows is a synthesis of the answer to my first research question, which aims at a descriptive understanding of the organizational and political-economic dynamics of the innovation process behind *sofosbuvir* and its pricing. In tracing the innovation process as it unfolded, *I argue that the prices of sofosbuvir were a product of financialization, a pattern of accumulation in which growth was pursued from the capitalization and control of intangible assets in financial markets.* This description helps us understand *sofosbuvir*'s price in the context of three empirical puzzles that emerged from my recounting of the innovation process.

- The first puzzle: how did Pharmasset, a company with no approved products or sales and an accumulated deficit of \$330 million over its 12-year existence, raise approximately \$100 million through venture capital and an IPO?
- The second puzzle: why did Gilead, with over \$8 billion in sales in 2011, bet \$11 billion for Pharmasset's *sofosbuvir* compound – and then direct the large majority of its eventual revenues from *sofosbuvir* to shareholders and a stockpile of cash?
- A third puzzle: why did Gilead's market capitalization (total share value) *halve* from its peak after *nearly doubling* its rate of profitability and accumulating \$30 billion in cash on the strength of their *sofosbuvir earnings*?

In each of these puzzles, different financial actors capitalized the anticipated earnings from hepatitis C assets (on the promise that downstream financial actors and health systems would 'value' *sofosbuvir* and its precursor, PSI-6130 at increasing prices) and gained control over them (either through share ownership, trading, or acquisition) in order to accumulate capital and generate near-term growth.²²⁹ This analysis of financialization, which I develop further below,

²²⁹ I used Veblen's work to define and conceptualize 'intangible assets' as well as capitalization in section 1.3.3. I traced these concepts in greater depth in chapter 4.

resolves each of the three puzzles – and situates *sofosbuvir*'s prices as a product of this pattern of accumulation. This pattern was in turn constituted by three dynamics, summarized in Table 6.1: (1) the mobilization of speculative capitals with the anticipation of rising prices and valuations for intangible hepatitis C assets in trading markets, (2) extraction driven by Gilead's shareholder control over growth expectations and distributions of capital, and (3) and governance of intangible assets and financial capital by a multi-valent state. My diagnosis of financialization stands in contrast to the dominant explanations of *sofosbuvir*'s prices: the prices of *sofosbuvir* did *not* represent the tangible costs of innovation, nor did they represent the embodied improvements in health experienced by patients and populations. I first describe my diagnosis through the dynamics that underpin it before returning later to the existing answers on drug prices.²³⁰

Table 6.1 The three dynamics constituting financialization of *sofosbuvir*

Dynamic	Key features
Mobilization of speculative capitals on anticipation of rising valuations in trading markets	<ol style="list-style-type: none"> 1. Speculative capitals set in motion by existence of downstream financial markets 2. Anticipation of rising prices and valuations for hepatitis C assets in these markets (capitalization) provided investors and traders to make capital gains. 3. Capitals entered for periods far shorter than the multiple stages and years required for drug development (compressed 'risk-reward loop'). 4. Almost completely reliant on external financial markets, Pharmasset positioned as a bundle of assets (a single asset, in this case) ready to be sold, rather than a durable business.
Extraction driven by shareholder control	<ol style="list-style-type: none"> 1. Shareholder control exposed Gilead to a structural crisis, driven by expectations of growth and disinvestment in innovation (i.e. distributions of capital to shareholders). 2. To respond to this structural crisis, Gilead mobilized accumulated capital to specialize in acquisitions – in this case of a late-stage asset, <i>sofosbuvir</i> – on the basis of charging patent-protected 'value-based' prices in the future. 3. This reinforced Gilead's position as an accumulation center – using its <i>sofosbuvir</i>-based revenues to stockpile cash for potential acquisition and distributed earnings to shareholders. 4. A 'cure market' eliminated the very growth prospects on which <i>sofosbuvir</i>'s value as an asset depended, intensifying Gilead's turn towards incremental improvements in a 'chronic market' to generate growth.
Governance of intangible assets and financial capital by multi-valent state	<ol style="list-style-type: none"> 1. Legislation permitted conversion of public knowledge into private, intangible assets (Bayh-Dole Act) that enabled <i>sofosbuvir</i> to be an object of speculation in financial markets. 2. Enabled emergence of speculative capitals through rule changes, beginning most prominently venture capital financing with Department of Labor 'prudent man' rule change in 1979 3. Sanctioned the distribution of capital from firms to shareholders through the promulgation of SEC rule 10-b-18 in 1982 4. Limited exercise of countervailing power on drug pricing by state has indirectly supported the reproduction of speculative and extraction strategies described in the first two dynamics highlighted above.

²³⁰ Appendix E contains a series of diagrams that depict parts of this innovation process, with the final diagram (the last page in the dissertation) attempting to illustrate the overall flows of capital, funding, and knowledge across the innovation process.

6.1.1. Mobilization of speculative capitals

Speculative capitals, coming in various forms from venture capital to institutional shareholders, mobilized behind Pharmasset on the promise of rising prices for better treatments (*pricing escalator*). In this process, patents (securing knowledge into intangible assets) drew in a chain of speculative financial actors pursuing the possibility of a significant reward by exiting long before the approval of any medicine, thereby passing off further risk to later investors and traders. Four key features of these speculative capitals are relevant to understanding *sofosbuvir*'s price: (1) their position in the innovation process, (2) the pricing and valuation logics driving them, (3) the expectation and time horizon of rewards, and (4) their consequences for the destination of Pharmasset.

First, these speculative capitals were 'doubly' set in motion by an entrepreneurial state and by the existence of downstream financial markets (both acquisition markets and stock markets) that could value intangible assets. On the one hand, venture capital mobilized based on the technological opportunity created by an entrepreneurial state, with the development of the replicon and the advance of nucleoside science.²³¹ Yet on the other hand, this speculative capital for Pharmasset - which came in multiple forms, from venture capital, corporate capital (Roche's partnership), and public equity (i.e. initial public offering) - was lured not on the revenues from a new product, but more on the potential for financial markets to value intangible assets through future capitalization, share trading, and acquisitions.²³² For venture capitalists, the presence of incumbent firms who might acquire Pharmasset as well as a stock market via which Pharmasset could become capitalized as a publicly traded company presented an opportunity to make a gain far before the uncertain fate of any particular pharmaceutical assets (Evnin 2014; Robbins-Roth 2001).²³³ Finally, institutional shareholders in the IPO and later equity traders bet on Pharmasset based largely on the potential for gains on near-term changes in share price on the NASDAQ stock market (Birch 2016).²³⁴

²³¹ I elaborate on the role of entrepreneurial state in 6.1.3 as well as in 6.2.

²³² In interrogating the 'Pisano puzzle' - referring to Gary Pisano's observation of a biotechnology sector that continued to attract capital in the absence of approved products and sales - Lazonick and Tulum mirror my analysis, positioning companies Pharmasset between an entrepreneurial state and financial markets (Lazonick and Tulum n.d.; Pisano 2006).

²³³ Even in Roche's partnership with Pharmasset, which did have the aim of taking PSI-6130 towards later stage clinical trials and regulatory approval, Roche exercised an ownership stake in Pharmasset as a way of mitigating their risk.

²³⁴ The emergence of these speculative capitals, such as venture financing, is linked to regulatory and political-legal shifts in the US State. For example, the Bayh-Dole Act and rule changes for pension funds

The second feature of these speculative capitals are the pricing and valuation logics driving them. The valuations in this speculative chain of capital were based on an anticipation of future earnings potential of an intangible asset with rising prices. This future earnings potential, on which different capitalists bet, rested on a promise of what I called the *pricing escalator*, in which investors and traders projected that buyers in the future would pay higher prices in exchange for medicines with improved clinical outcomes (Gregson et al. 2005; Vernaz et al. 2016). This echoes Veblen's analysis of intangible assets in the economy, with value coming not from existing approvals and sales, but from ownership and control over future earnings streams that contain the promise of differential accumulation – gaining more than competing avenues for accumulation (Gagnon 2016; Veblen 1908a). This pricing escalator underpinned the growing market valuations for hepatitis C assets during the 2000s, as larger patient populations were forecasted to be eligible for treatment with progressively improved regimens (Ha et al. 2011; Pharmasset 2009).

In 2004, for example, when Pharmasset raised its biggest venture capital round (series D), the company had already run \$15 million in deficits, and was not expected to have an approved product in the near future (Pharmasset 2006). But they had recently patented a hepatitis C compound, PSI-6130. At the time, Roche had their interferon-based treatment on the market for approximately \$36,000 per patient for a toxic, year-long regimen. Pharmasset and their investors anticipated that developing a directly acting anti-viral, rather than interferon-based regimen (which operated indirectly by boosting the body's immune system), would lead to more patients desiring and being eligible for the treatment (fewer side effects, shorter treatment) (Pharmasset 2006; 2009).²³⁵ This offered investors and companies a chance at winning the intra-capitalist competition not only for profits, but for *growth* – to make more money than the owners of the existing standards of care at the time, Roche and Schering Plough.²³⁶ Such forecasts required an

and capital gains taxation in the late 1970s and early 1980s expanded financial flows to venture capital. I turn to this in section 6.1.3.

²³⁵ While these longer-term expectations held up sustained valuations in financial markets, equity traders attempted to make gains by betting on Pharmasset's nearer-term milestones and news announcements. The launch of a new clinical trial or new results for a compound drove short-term swings in Pharmasset's share price from which traders attempted to make capital gains. For example, when Pharmasset announced part of the Phase II trial results for PSI-7977 in March of 2011, the company's share value rose by 24% in a single day – this climb ultimately shaped Gilead's acquisition price-tag later in the year (Feuerstein 2011)

²³⁶ The revenue opportunity ('the market') was defined by price x eligible patient population. Even with a higher potential patient population, investors do not assume lower price (offset by the higher potential volume). Instead, they make investments on the idea that 1) growing revenue will enable a given asset vehicle or company to generate a differentially greater accumulation than the existing asset (Roche's

anticipation of the relationship between manufacturers and buyers (publicly funded health delivery systems) with regards to drug pricing, to which we return in the following section (6.1.2).

Third, investment and trading in Pharmasset was defined by a compressed ‘risk-reward loop’, in which capital entered into the innovation process for periods far shorter than the multiple stages and years required for drug development. Investors and traders risked their capital for the sake of uncertain rewards, yet these risks and rewards were variable, depending on the expectations and interests of a given investor or trader. What these variable investors and traders shared – from venture capitalists to institutional shareholders at the time of an IPO, for example – were ‘exit possibilities’ at a ‘terminal point’ long before the approval of any new medicine. Drug development can last well over a decade – the case of *sofosbuvir* took 10 years, between Pharmasset and Gilead.²³⁷ But these different forms of speculative capital were only advanced into the innovation process for fractions of this time: the risk-reward return-loop was compressed into a period that lasted a few years in the case of venture capitalists to hours or days, in the case of stock traders betting on Pharmasset’s share price. The liquidity offered in such a model, in which investors can enter and exit at variable points and with compressed time horizons, is sustained by the pricing possibilities and valuation promises described in the previous point (Andersson et al. 2010; Birch 2016). Andersson (2010) and Birch (2016) have described this process of investment to be akin to a ‘relay-race’, in which different financial actors take the baton of drug development. Yet where all the actors in a relay race win a medal for their collective labors, this financialized model diminished the relationship between the actors taking risks and those actors accruing rewards. We return to this risk-reward nexus in section 6.2.

Finally, the dynamics of speculative capital-oriented development with complete reliance on external sources of financing and little retained capital for reinvestment meant that *Pharmasset was not positioned to become a durable organization with multiple integrated capabilities* (research, manufacturing, regulatory affairs, distribution) (Andersson et al. 2010; Hopkins et al. 2013). *Rather, Pharmasset was more a bundle of assets ready to be sold.* By the time Pharmasset had developed PSI-7977 into Phase II trials, the company had yet to turn a profit – and had accumulated a deficit of more than \$300 million over its life-span (Pharmasset 2011). Yet its value in the summer of 2011 had reached ~\$8 billion based on the promise of the compound

interferon regimen, for example), and 2) health systems, including the state, will pay based on a ‘value-pricing’ rationale, which I describe elsewhere in detail.

²³⁷ The ten-year figure comes from the period beginning in 2003, when Pharmasset began working on PSI-6130, the precursor to *sofosbuvir*, to 2013, when Gilead received FDA approval for *sofosbuvir*.

and resulting revenue opportunity. Pharmasset's life cycle and valuation illustrates Mirkowski's description of such small, product-less biotechnology companies as 'financial artefacts' (Mirowski 2012:296). As Pharmasset scanned the horizon for its future, incumbent firms like Gilead Sciences appeared less ideal as competitors and better as potential suitors. In this respect, Pharmasset was positioned to be what Blackburn (2006:42) has called a 'disposable' business, with the organization dissolving on the sale of its assets.

These four features together reveal a mobilization of speculative capital oriented around financial gains from betting on an intangible pharmaceutical asset for periods far shorter than required for the development and use of *sofosbuvir* as a hepatitis C therapy. The anticipation of patent protected pricing propelled growing financial market valuations for hepatitis C assets, in which investors and traders forecasted buyers in the future paying higher prices in exchange for better clinical outcomes. This mobilization of speculative capitals, however, would be interrelated with the capital allocation strategies of large, incumbent pharmaceutical companies, to which we turn next.

6.1.2 Extraction driven by Gilead's shareholders

To overcome episodes of recurring crisis driven by shareholders' expectations of growth and distributions of capital, Gilead used its pricing and revenue to position itself as an 'accumulation center' in the innovation process, with stockpiled revenues used for speculative bets on late-stage assets through acquisitions as well as extraction by shareholders through buybacks and dividends. This orientation to extraction is illustrated by four elements structuring Gilead's position and function in the innovation process: (1) a recurring configuration of crisis driven by shareholder control and expectations of growth, (2) the generation of growth as an acquisition specialist, with a pricing strategy culminating the pricing escalator that had mobilized the chain of speculative capital behind *sofosbuvir*, (3) the reproduction of a financial cycle using accumulated revenues from *sofosbuvir* on speculation and extraction, and (4) an intensification of these dynamics with ownership of a curative 'asset' which eliminated the very market for growth (by curing patients) on which its value as an asset rests.

First, shareholders and financial markets exposed Gilead, even as a company with high rates of profitability, to a structural crisis. This structural crisis was a product of the 'shareholder growth treadmill', in which shareholders expect differential growth (greater than the cost of capital and competing companies) on a near-continual annual basis (Montalban and Sakinc 2013;

Rajan 2012).²³⁸ In other words, what will make the most money in the fastest time? In this way, publicly traded companies like Gilead are less valued by their profitability and approved products, and more on their potential to deliver this growth (Birch 2016; Birch and Tyfield 2013; Rajan 2012). For example, even with rates of profitability annually between 20-30% in the 2009-2011 period, Gilead's share price plateaued on the perception that their HIV-centered business would not generate further growth. Convergent with patent cliffs on their existing HIV assets as well as a dry pipeline lacking investment, this expectation of shareholder-driven growth produced recurring episodes of crisis for Gilead. This shareholder control over business strategies has been in part the product of several regulatory shifts promulgated by the US state since the 1970s, which has enabled the distribution of capital towards shareholders and tied the short-term interests of shareholders to corporate executives (Lazonick 2015; Stout 2013).²³⁹ The expectations of shareholders motivated Gilead's senior leadership to look for growth from pharmaceutical assets in financial markets described in the previous section (6.1.1).

This brings us to the second element: to respond to crisis, Gilead mobilized its accumulated capital less as a research and development company and more as an acquisition specialist with significant power vis a vis the health delivery state in terms of drug pricing. With Pharmasset's PSI-7977 demonstrating positive outcomes in Phase II trials, Gilead aimed at gaining the ownership and control over the sizeable flow of future earnings the compound promised (United States Senate, Committee on Finance 2015; Veblen 1908b). The company used a portion of its \$10 billion in accumulated capital from HIV sales to make an \$11.2 billion bet on Pharmasset for its PSI-7977 compound, getting the rest of its capital for the transaction by leveraging its accumulated capital to raise debt (Gilead Sciences 2012; S&P Capital IQ 2012). In its capitalization exercise to value PSI-7977, Gilead projected charging over \$65,000, continuing the pricing escalator that mobilized the chain of speculative capital earlier in the innovation process (United States Senate, Committee on Finance 2015). As Veblen initially illuminated, Gilead's capitalization exercise showed the relations of power at stake in the innovation process with regards to drug pricing: to make bets, capitalists anticipated a state that would continue to pay higher prices in exchange for therapeutic

²³⁸ This structural crisis can be viewed through the hybrid combination of Veblen's insight into capitalists pursuing differential accumulation vis a vis other potential vehicles for accumulation (magnitude of growth) with the insights of shareholder-oriented financialization, in which shareholders expect this growth in quarterly and annual periods (velocity of growth) (Cochrane 2011; Davis 2009; Lazonick et al. 2016; Nitzan and Bichler 2009).

²³⁹ I provide a fuller summary of these shifts in sections 4.2.2 as well as 1.3.2.

outcomes (Gagnon 2016; Veblen 1908b). Lobbying clout, both by Gilead as an individual business but also by the pharmaceutical industry as a whole, sought to maintain this relation of power with the US state (Demko 2014; OpenSecrets 2017). Gilead's launch pricing, ultimately set at \$84,000 and \$94,500 for its *sofosbuvir*-based regimens, culminated the pricing escalator and enabled the company to accrue \$45 billion in revenue in its first three years since approval – the most profitable drug launch in history.

This revenue from sofosbuvir-based medicines reinforced the third element: Gilead's position as an 'accumulation center' to speculate and extract value for shareholders. Gilead accrued gross profits of \$76 billion between 2014 and 2016, growing from annual revenues of \$11 billion in 2013 to \$32 billion by 2015. These financial outcomes demonstrate Zeller's (2007) conception of multi-national pharmaceutical companies existing as 'accumulation centers', with growing stockpiles of cash drawn from monopoly rents on their ownership of assets. Where did this accumulated capital go? Gilead's strategy reflects Lazonick's analysis of the influence of shareholder value on companies shift from strategies of 'retain and reinvest' earlier in the 20th century to 'downsize and distribute' in recent decades (Lazonick 2015; Lazonick et al. 2016). At the end of 2016, Gilead held \$32.4 billion in cash (after ending 2013 with \$2.6 billion in cash), largely on the growth from its hepatitis C revenues (Gilead Sciences 2017). Shareholder and investment analysts in financial markets expect Gilead to use this accumulated capital to acquire a pharmaceutical asset that can generate further growth (Crow 2015; Nisen 2017).²⁴⁰ In the meantime, Gilead also distributed \$30.7 billion to shareholders in the form of buybacks and dividends (with \$26.3 billion of this in buybacks). These distributions were reinforced by the fact that Gilead's senior leadership were major stockholders themselves, with the top five senior executives accruing over \$1 billion in compensation in the three years following the launch of *sofosbuvir* (Gilead Sciences 2016b). Only \$9.6 billion was directed towards research and development within the company, primarily on late-stage trials for re-combinations of its existing HIV and hepatitis C medicines (Gilead Sciences 2017).²⁴¹

²⁴⁰ Though the company has yet to make a major acquisition at the time of this dissertation submission, pressure from financial markets on Gilead's leadership to pursue such a transaction has grown, for reasons I illustrate in the fourth point below.

²⁴¹ As I documented in chapter 5, this dual strategy of speculation and value extraction rather than internal investments in research was summed up by Gilead's CEO declaration of its strategy in a 2016 earnings call: "For us its fairly simple. We have the flexibility to do both things; that is, return shareholder value through stock repurchases and dividends and of course continue to be opportunistic in M&A (mergers and acquisitions)" (Seeking Alpha 2016c).

Finally, far from inoculating itself against crisis, Gilead's accumulation with sofosbuvir revealed a fourth point: a cure eliminates the very market for growth on which its value as an asset depends, thereby intensifying the company's extractive and speculative strategies. Despite Gilead's high rates of profitability in 2015 and 2016 – at 55% and 45% respectively – the company's share price fell from its peak of \$122 in 2015 per share to almost \$60 by early 2017 (Crow 2016a; Nisen 2017). This juxtaposition of high profitability with declining share price is captured by Veblen's analysis of assets, in which valuation is based on the potential generation of differential growth in the future (Birch 2016; Veblen 1908a). The anticipation of sliding towards a 'patient cliff' created another episode of crisis for Gilead. In responding to their declining prospects for growth, Gilead has directed capital to marketing for hepatitis C as well as clinical trials aimed at incremental improvements in HIV order to extend intellectual property protection over this 'chronic market' (see chapter 5).²⁴²

In sum, as a publicly traded incumbent pharmaceutical company, Gilead was valued by shareholders based on potential *growth* from pharmaceutical assets rather than profitability from products, which generated a process of extraction, accumulation, speculation in attempts to transcend recurrent episodes of crisis.

6.1.3 Governance of intangible assets and financial capital by a multi-valent state

Finally, these two mechanisms of financialization – the mobilization of speculative capital and extraction driven by shareholders – were underpinned by a third: the governance of intangible assets and capital by a multi-valent state.²⁴³ Investments by an entrepreneurial US state produced the intangible assets that mobilized the private capital documented earlier; state governance also influenced the trajectory and uses of these intangible assets (such as Pharmasset's nucleoside science) as well as private capitals (such as venture capital). I do not argue whether the relationship between the state and the financialization of biomedical innovation was a result of regulatory bias and capture by industrial interests, voluntary and intentional policy shifts pursued by the state, or inadvertent attempts to solve problems in other

²⁴² See Joseph Dumit's (2012a) book *Drugs for Life* for a wider discussion on how current models of public health epidemiology and financial market oriented drug development converge to promote 'chronic therapies'.

²⁴³ By a multi-valent state, I refer to the multiple state organs that influence the innovation process, from innovative, investment organizations such as the NIH to regulatory bodies such as the Securities and Exchange Commission. By governance, I mean both legislation passed through the US Congress as well as rules promulgated and changed by agencies with regulatory power, such as the Department of Labor.

domains of policy – or potentially (and likely) some combination of all of the above.²⁴⁴ However, I observed that these ‘rules for capital’ governed by the state underpinned each of the first two mechanisms I elaborated in this chapter. Taken together, the case highlighted four domains of state governance (summarized in Table 6.2) which contributed to the financialization of the innovation process behind *sofosbuvir*.

Table 6.2 A multi-valent state and the financialization of *sofosbuvir*

State influence over rules of control	Government legislation and rule-making
(1) Conversion of public science into private assets	- 1980 Bayh-Dole Act provided the political-legal contract for conversion of publicly funded knowledge into private intangible assets that entered into financial markets and became objects of speculation and shareholder control. ²⁴⁵ (Kesselheim 2011; Rai and Eisenberg 2002)
(2) Emergence and expansion of venture capital and financial markets for speculative capitals	- Department of Labor ‘prudent man’ rule amendment (1979) – enabled pension funds to use larger shares of its capital (up to 5% at the time) in venture funds, considered to be higher-risk; led to rapidly expanding flows of capital from pension funds (a type of institutional shareholder) to venture capitalists. (Gompers 1994) - Reduction in capital gains tax (initial major reduction in 1978, later reductions in 1980s – 2000s) (Gompers 1994) - NASDAQ (founded in 1971) permits IPOs and trading on startups with no products or profits and low capitalization, with SEC as the regulatory agency mediating and monitoring main rules ²⁴⁶ (Lazonick and Mazzucato 2013)
(3) Increased distribution of capital from business organizations to shareholders	- SEC Rule 10-b-18 (1982), permitting companies to use capital to repurchase (buy back) their own shares on the open market with out being charged with share price manipulation; share buybacks escalated in the 1990s and 2000s as a ‘flexible’ way to distribute capital to shareholders (Lazonick 2015)
(4) Payment for increasing prices by health delivery state with limited use of countervailing negotiating power or regulation	- Medicare Part D (2004) bars government from using negotiating power with manufacturers (Bach 2009) - Medicaid program designed as a state-based program, fragmenting negotiating power (Barua et al. 2015) - No uses to date of ‘march-in rights’ contained in Bayh-Dole Act (Rai and Eisenberg 2002; 2016b) - Turn towards value-based payment (in which increase in prices are tied to therapeutic improvements) (Bach and Pearson 2015)

²⁴⁴ I discuss this as a potential direction for further research in section 6.4.

²⁴⁵ The knowledge patented through the Bayh-Dole Act provisions is also governed by other features of the US state’s approach to intellectual property: (1) through the US Patent and Trademark Office, patents are granted for 20 years from the point of issuance, as well as (2) FDA measures to protect the data generated in clinical trials (‘data exclusivity’ through 1984 Hatch-Waxman Law) in order to delay generic competition.

²⁴⁶ See SEC site for history of its rule-making for the NASDAQ stock market:
<https://www.sec.gov/rules/sro/nasdaq.htm>

The first domain of state governance was the rules of control over intangible assets. In the case of *sofosbuvir* and hepatitis C, investments by the US state produced the replicon research tool and the nucleoside science that were used by Pharmasset for their development of *sofosbuvir* (see chapter 3, and Talbe 3.1). The governance of intangible assets by the US state, through the 1980 Bayh-Dole Act passed by Congress, enabled Ray Schinazi – the founder of Pharmasset – to convert this publicly funded science into privately owned intangible assets (Kesselheim 2011; Rai and Eisenberg 2002). With this political-legal arrangement, Pharmasset emerged from the VA and Emory-based labs at which Schinazi had been based, and attracted private capital to finance the further development of their intangible nucleoside assets.

Second, the state governed the rules for the emergence and function of speculative capitals that mobilized behind Pharmasset. Schinazi did not take his inventions to a larger, established company; rather, the conversion of public science into private assets as permitted by the Bayh-Dole Act coincided with rule changes that had expanded the role of venture capital to be a main early-stage source of financing for these private assets (beyond the state). With regards to the expansion for venture capital, for example, the Department of Labor in 1979 changed the ‘prudent man’ rule which allowed pension funds to direct a greater percentage of their capital to venture funds (Gompers 1994). Furthermore, US Congress passed a major reduction in capital gains tax the same year, which may have also expanded venture capital (Gompers 1994). By the time Pharmasset began in the late 1990s, the maintenance of these rules positioned venture capital to become a key source of financing for small biotechnology companies (Pisano 2006; Robbins-Roth 2001). The later transformation of Pharmasset from a privately held, venture-backed company into a publicly traded company, even with no profits or approved products, was also facilitated by a state-mediated financial actor: the NASDAQ stock exchange. A product of SEC-guided moves to promote stock trading in the 1970s, NASDAQ allows companies with low capitalization and little to no profitability to join the exchange (Lazonick and Mazzucato 2013). NASDAQ has provided a market for raising financing from institutional shareholders and trading on intangible pharmaceutical assets. The creation of these financial markets was also paralleled by a stark absence of the state in terms of the public financing of clinical trials (Baker 2008). Lacking access to further mission-oriented public funding from the state, Pharmasset instead relied on speculative capitals external to the firm.²⁴⁷

²⁴⁷ Though the NIH supported an important Phase II trial for *sofosbuvir* (Osinusi et al. 2013a), the US state had not developed a larger funding mechanism for hepatitis C clinical trials, leaving a small cash-hungry

Third, the late 20th century rise of shareholder control over the capital allocation decisions of established companies was mediated by several factors, and I focused on one in particular – SEC’s Rule 10-b – given Gilead’s use of share buybacks as central to their business strategy. Rule 10-b permitted companies to buy a significant amount of their own shares, which Gilead’s senior executives, as major shareholders themselves, pursued as a ‘flexible’ strategy to distribute capital to its shareholders while maintaining the rest of their accumulated capital for potential acquisitions (Lazonick 2014). The buyback rule facilitated ‘maximizing shareholder value’, in which shareholders not only expected near-term and differential growth but also the distribution of ‘residual’ capital that could not be used to yield this type of growth (Lazonick 2015).

Fourth, the US health delivery state exercised limited power in drug price negotiations as a main buyer of sofosbuvir-based medicines. Though the state’s governance of drug pricing regulations did not directly influence the control over capital, it did so in an indirect manner: the anticipation of the state’s payments of higher prices fueled the speculative bets made by financial actors – from venture capitalists to institutional shareholders – along the chain of innovation. Notably, Gilead’s accumulated capital from the payments made by the state was ultimately directed towards the acquisitions and buybacks illustrated earlier. The limited exercise of the state’s countervailing power came in multiple forms, from the fragmented state-based Medicaid system lacking market power as well as federal systems like Medicare legally barred from negotiating directly with manufacturers (due to the 2004 passage of the Medicare Part D program by a Republican-controlled Congress) (Bach 2009). Even in the case of a major public health concern, the US state has also never invoked the ‘march-in’ provision contained in Bayh-Dole Act, whereby the government can license knowledge property to a third-party manufacturer in order to meet a given social concern (Silverman 2016d). This limited exercise of countervailing power has remained true in the case of *sofosbuvir* and hepatitis C.

In sum, the state’s governance of the rules by which intangible assets and different capitals function in the economy – from venture capital to the accumulated capital of businesses – played a critical role in the financialization of the innovation process and prices behind *sofosbuvir*.

company like Pharmasset pursuing venture capital, public equity markets, and potential acquirers. Even if the company had received additional public funding, however, the state would be constrained by a second factor beyond narrow financing: the absence of rules for public ownership stakes in companies granted entrepreneurial investments from the state. Though Pharmasset already counted the Veterans Administration as well as the NIH as two crucial sources of support in its early stages, neither possessed an ownership stake in the company, leaving the state unable to share in the financial upside of the innovation process as venture capitalists, for example, did.

Rather than pursuing further public financing for drug development, Pharmasset relied on capital from outside the firm in the form of short-term oriented financing. Furthermore, the rules of shareholder control and distributions of capital focused Gilead less on research and development company and more towards acquisitions and buybacks. Finally, the health delivery state's limited countervailing power vis a vis end-stage manufacturers, in this case Gilead, sustained this mobilization and distribution of capital in the innovation process.

This innovation process thus illustrated a multi-valent state operating in different domains of the economy, from innovative, public sector organizations producing intangible assets to an array of bodies with regulatory power (i.e. SEC, Department of Labor, Medicare) governing the rules for the distributions and uses of these intangible assets as well as different kinds of capital.

6.1.4 Summary of the three dynamics and revisiting existing answers on drug prices

The financialization of biomedical innovation in the case of *sofosbuvir* – as a pattern of accumulation in which growth was pursued from the capitalization and control of intangible assets in financial markets – was underpinned by three dynamics: the mobilization of speculative capitals from investing and trading on the anticipation of higher prices and valuations (the pricing escalator), extraction driven by shareholders pursuing growth and distributions of capital, as well the governance of intangible assets and financial capital by a multi-valent state. With these processes, the prices of *sofosbuvir* became fastened to the logics, institutions, and relations of power propelled by financial markets, rather than the tangible costs of production and innovation or the value of the embodied health experiences of patients infected with hepatitis C.

This diagnosis departed from existing answers on drug prices by analyzing the innovation *process* behind *sofosbuvir* and the organizational as well as political-economic dynamics that made up this process. Rather than focus on 'risk' and 'value' at the point of exchange between Gilead and health systems, for example, I elucidated the dynamic nature of these concepts across the innovation process – such as strategies of risk-mitigation undertaken by different actors and the *creation* and *extraction* of value. Rather than study the monopoly-state relationship in isolation of other factors, I situated this relationship in the wider context of shareholder control over Gilead's business strategy as well as the ownership of intangible assets in financial markets. In reducing our understanding of drug prices to a single relationship and point of exchange, these

existing answers had obscured the influences and consequences of crucial organizational and political-economic dynamics.

By contrast, my organizational and political-economic orientation to understanding an innovation process also afforded me the opportunity to more fully evaluate its outcomes - through assessing the distribution of risks and rewards across the process, the direction and sustainability of innovation, and impacts on patients and public health. This evaluation further illuminates the limits of existing answers on drug prices by indicating the distributive consequences of financialization. Before revisiting existing answers on drug prices to show the analytical ground gained through my account of the innovation process (which I do in section 6.3), I next turn to this opportunity of evaluating its outcomes.

6.2 Evaluating the outcomes of the process

Having described the processual mechanisms and relations of power underpinning the prices of *sofosbuvir* based medicines, I now take on a second task: an evaluative assessment of the innovation process. To answer my second research question, I posited several key measures by which to make this assessment. First, I aimed to take stock of the distribution of risks and rewards across the process, using Lazonick and Mazzucato's (2013) risk-reward nexus as a framework for analysis. Second, I accounted for the implication of such a distribution on the *direction* and *sustainability* of the innovation process, as well as its impacts on patient and public health outcomes. I argue that while entrepreneurial investment from the state shaped the direction of the innovation process towards a cure, the processes constituting financialization disconnected the link between risk-taking and the accrual of rewards, undermined the sustainability of the innovation process, and diminished the patient and public health outcomes for a communicable disease. I take each assessment in turn.

6.2.1 The distribution of risks and rewards

The case of *sofosbuvir* illustrates a disconnect between the distribution of risks and rewards across the innovation process. Multiple actors took on risks for the sake of uncertain rewards along this innovation process, but the risk-reward ratio varied for different actors.

For example, the case of *sofosbuvir* and hepatitis C reflects Mazzucato's conception of the role of an entrepreneurial state in innovation processes (Mazzucato 2013b; 2016). Public sector organizations, primarily the US National Institutes of Health, provided patient capital and risk-

taking investment for *sofosbuvir* and hepatitis C which included (see Table 3.1): (1) long-term tracking studies of the disease to reveal its significant clinical and public health consequences as well as its identity as a pathogenic virus, (2) the development of the replicon tool, which pushed the technological frontier for all hepatitis C drug development and shaped a ‘market’ for private investment, (3) the funding of nucleoside science through Schinazi’s VA and Emory-based laboratories during the 1990s and early 2000s. Beyond these critical early-stage inputs, the state also (4) funded the early-stages of therapeutic development that would lead to the pre-cursors of *sofosbuvir* through the NIH’s SBIR grants to Pharmasset.²⁴⁸ Yet the health delivery state also paid Gilead’s monopoly prices for a downstream outcome of those public investments, while receiving no direct return on their initial investments and only diminished indirect returns via taxation due to Gilead’s offshoring of intellectual property for *sofosbuvir* to Ireland (see chapter 5).

On the other end of the spectrum, Gilead accrued a major reward: \$45 billion in revenue from *sofosbuvir* between 2014 and 2016. But Gilead then directed much of this capital towards its shareholders, who had collectively not risked any capital into the innovation process for *sofosbuvir*.²⁴⁹ Among these shareholders were Gilead’s senior leadership: the top five executives in total earned over \$1 billion in compensation in the three years since *sofosbuvir*’s launch, with over 90% of their compensation coming in the form of stock awards and options (see chapter 4).

Venture capitalists and Pharmasset’s initial public shareholders for the IPO as well as shareholders in their follow-on financings each risked capital behind Pharmasset, with a share of this capital going to the development of *sofosbuvir*. The existence of financial markets, however, enabled each of these investors to enter and exit their investment and ‘cash out’ long before the approval of any product, thereby mitigating their risks by passing along ownership claims while attempting to maximize their potential rewards by wagering bets at the right time (Andersson et al. 2010; Birch 2016; Gleadle et al. 2014). The innovation process behind *sofosbuvir* recalls Birch’s (Birch 2016:465) observation that the financing of biotechnology and drug development is akin to

²⁴⁸ Publicly funded science in Europe, available in the public domain, also provided the critical knowledge (the ‘MgGuigan method’) that activated *sofosbuvir*’s previously indolent precursor, PSI-6130, into a curative backbone. The NIH and the Affordable Care Act – through the Internal Revenue Service – also funded Phase II trials for *sofosbuvir*.

²⁴⁹ The \$11.2 billion acquisition of Pharmasset as well as the late-stage trials completed by Gilead were funded by retained earnings from prior revenues on HIV medicines (as well as debt that was leveraged using this cash) paid by public health systems. Furthermore, Gilead had last raised investment capital from shareholders in 1996, and given that the company began to offer a dividend only in 2015, those shareholders have likely left their ownership claim long ago.

a ‘reverse Ponzi scheme’, in that the final financier can accrue the largest return, while the first financiers (the government, friends and family in the seed rounds) accrue the least. As I described earlier, this disconnect between risks and rewards can be traced to relations of power between state, businesses, and financial actors.

This accounting of the *sofosbuvir* process provides positive evidence for Lazonick and Mazzucato’s (2013:1095) claim that, “although risk-taking has become more collective [...] the reward system has become dominated by individuals, who inserting themselves strategically between the business organization and the product market or a financial market, and especially the stock market, lay claim to a disproportionate share of the rewards of the innovation process”. This outcome was starkest with Gilead’s shareholders, who accrued a large share of rewards by being positioned at the end-stages of the innovation process. However, what kind of outcomes did this distribution of risks and reward in the case of *sofosbuvir* produce for the direction and sustainability of biomedical innovation as well as for impacts on patient and public health?

6.2.2 Implications for the direction and sustainability of biomedical innovation

In evaluating the innovation process, I first map the implications of the risk-reward nexus described above onto both the *direction* and *sustainability* of the innovation process. These measures are intertwined. On the one hand, as argued by Stirling (2009) and Mazzucato (2016) innovation has not just a rate but a direction: in the realm of biomedicine, an example is the creation of better quality therapies that can improve clinical outcomes and address public health challenges. The extent of this directional outcome - such as whether an innovation process only incrementally improved outcomes or produced breakthroughs – can be assessed. On the other hand, innovation is also a process that is continually dependent on capital and labor across multiple stages of discovery, development and deployment as well as for numerous health challenges, and thus can be evaluated for whether its directional outcomes (in this case, a curative therapy) can be reproduced in a sustainable manner for other areas of unmet medical need.

With regards to the *directional* outcome, I begin my analysis by acknowledging a fact of the *sofosbuvir* case that is rare in biomedical innovation: a *curative therapy* was developed for patients which can be taken largely free of side effects and eliminates the need for long-term, chronic treatment. This represents an optimal directional outcome for the hepatitis C innovation process: rather than producing an incremental advance, these medicines created a paradigm shift for patients. Yet the valorization of Gilead for this outcome, can, however, obscure the key factors

behind it and lead to mis-recognizing *how* the direction of the innovation process was shaped and might be *sustainably reproduced*. A health economist at USC, Dana Goldman, reflected this mis-recognition when he shared in an interview with an online news site, “We’d love for pharmaceutical companies to come up with a treatment that cures diabetes rather than just treats it. I want to pay them enough so it’s possible they’ll start working on cures rather than treatments” (Kliff 2014). Goldman’s stated hope of creating more curative medicines by focusing only on payments to Gilead falls short on two counts, each of which demonstrate the ways in which state, business, and financial actors influenced the *direction* and *sustainability* of the innovation process in the case of hepatitis C and wider areas of unmet medical need.

First, an entrepreneurial state, primarily in the US, provided four critical inputs that set the direction of the innovation process towards a cure: (1) unveiling the virus and its biology as a pathogen of public health concern but also amenable to elimination through its long-term tracking studies, (2) development of the replicon, with which companies tested antivirals that directly attacked and eliminate hepatitis C unlike prior interferon therapies²⁵⁰, (3) long-term investments in nucleoside science that gave Pharmasset the scientific base with which to eventually develop *sofosbuvir*, and (4) the European supported ‘Protide method’, which enabled *sofosbuvir* to reach the liver and was the differentiator from other previous attempts at creating compounds with high cure rates.

Yet the public-sector actors that enabled the directional outcome of a curative therapy realized diminished rewards from the process, which can threaten future investments in the uncertain research on which such directional outcomes rest. In other words, the sustainability of the innovation process is at stake: failing to reward the value creating organizations that shaped this directional outcome in a given process may challenge future value creation in the form of breakthrough therapies. As I documented earlier, neither the VA nor the NIH gained an ownership stake in Pharmasset to share in the upsides of the company’s gains that could have financed future innovation efforts, even though both public sector organizations provided long-term support to the science on which Pharmasset was founded (see Appendix B and chapter 3). Furthermore, Gilead avoided \$10 billion in taxes in the first two years after its *sofosbuvir* launch,

²⁵⁰ Of these four inputs, the replicon was most pivotal towards setting the direction towards a curative therapy, as drug developers could thereafter test antiviral compounds that directly eliminated the virus, rather than therapies that worked indirectly to boost the immune system. The direct targeting of the virus was necessary for the high cure rates observed with *sofosbuvir* (Bartenschlager 2002).

challenging the tax base used to finance the public-sector organizations that supported innovation efforts (Kocieniewski 2016). Gilead's tax avoidance over two years (2014-2015) was equivalent to 1/3 of NIH's annual budget, which has hovered in the ~\$30 billion range in recent years (NIH 2017a). Proposed cuts to the NIH budget in the US along with reductions in corporate taxation currently being debated within the US political arena are an exacerbation of this dynamic (Varmus 2017).

Second, rewarding the end-stage manufacturer (Gilead) with more capital, as Goldman suggests, reinforced late-stage speculative and extractive strategies that were more captured by logics and directions of continual revenue growth rather than directional outcomes such as breakthrough therapies. This has implications for the sustainability of capital allocation across multiple areas of unmet medical need. In the context of this cure market, we observed that Gilead, beyond distributing much of its revenues from hepatitis C to shareholders in the forms of buybacks and dividends, also re-directed their hepatitis C capital towards clinical trials for incremental improvements to HIV/AIDS medicines, which are chronic, life-long treatments with 'sustainable' growth projections. Paying more to Gilead for a cure, therefore, has not ensured – per Goldman's hope – that more money is going towards cures rather than chronic therapies. In fact, through its HIV strategy, I illustrated that *Gilead is dis-incentivized to invest more money towards cures under the conditions of financialization*. This dynamic supports Dosi's (1982) claim that markets are "blind" to directional outcomes that may relate to societal challenges.

The pricing and valuation strategies underpinning the distribution of risks and rewards in this innovation process also produced another outcome: an affordability crisis for health systems, which threatened the directional possibility at the heart of better quality therapies: realizations of improved patient and public health outcomes, and in the case of hepatitis C, the elimination of an infectious disease. We turn to assessing this set of outcomes next.

6.2.3 Patient and public health outcomes

The existence of a curative therapy with few side effects offered a stark break from prior treatment regimens. For patients, *sofosbuvir* represented a breakthrough and cause for hope. For policy-makers and public health officials, these medicines also offer the possibility of halting transmission of the virus and reducing the prevalence of the disease at a population level (Ward and Mermin 2015). Yet these hopes have ebbed in light of the prices of *sofosbuvir*-based medicines. As I documented in chapter 6, health systems around the world have restricted access

to the medicines due to their price and resulting budgetary pressures. In the US during 2014-2015, about 230,000 patients *could* get access to the medicines through public health systems, but this represented a fraction of the nearly 1.3 to 2.4 million patients on publicly funded insurance believed to be infected (Chahal et al. 2016; Edlin 2016; Edlin et al. 2015; United States Senate, Committee on Finance 2015).²⁵¹ The much touted ‘value’ of these medicines – particularly if used to treat patients most likely to transmit the disease as well as those in early stages of disease most likely to progress to later stages – was diminished by the pricing strategy employed by Gilead and the inability of government health systems to negotiate better deals. In chapter 5, I illustrated three impacts on patient and public health consequent to the innovation process and pricing of *sofosbuvir*-based medicines.

First, restrictions in access to *sofosbuvir*-based medicines have meant that many patients infected with hepatitis C are waiting for the treatment. These restrictions, based on liver staging and substance abuse, have disproportionately affected those populations most vulnerable from infection, transmission, and progression of the disease (Beckman et al. 2016; Rosenthal and Graham 2016; Ward and Mermin 2015). The systems of state and federal prisons, for example, in the US, has yet to offer widespread access to treatment. Only 949 patients out of a total of approximately 106,000 patients in the US prison system were believed to have received treatment in the years 2014 and 2015 (Beckman et al. 2016). Yet the incarcerated population is disproportionately at risk of not only being infected with hepatitis C, but also transmitting the disease in the community upon release (Barry-Jester 2015). The deployment of the medicines has thus exacerbated the social gradients along which the disease runs, with higher income patients with private insurance more likely to get the medicine (Re et al. 2016). These restrictions have meant that many patients are unable to break free both from the pathophysiology of the disease and the stigma that the infectious disease carries (Harris et al. 2015; Rhodes et al. 2013). In some cases, patients decided not to wait and instead turned to older, more toxic therapies, exposing them to the risk for deleterious side effects and a reduced chance of realizing a cure (Harris et al. 2015; Rhodes et al. 2013).

Second, at the level of health systems, public health plans for hepatitis C elimination have been delayed and deferred, as officials scramble to figure out how to fund treatment as part of such a plan. The US Institute of Medicine commission dedicated to developing such a plan

²⁵¹ See Chapter 5, section 5.2 for more on these outcomes.

declared in 2017 that without the government licensing the intellectual property from Gilead Sciences to a generic manufacturer, the country was unlikely to realize a goal of eliminating the disease by 2030 (National Academies of Sciences, Engineering 2017). Modelling studies have confirmed this forecast (Roy et al 2016a). By contrast, Gilead's deal with the Egyptian government, in which they have licensed the medicine for less than a \$1,000 per three-month regimen, has allowed the country to launch an ambitious hepatitis C elimination campaign (McNeil 2015). This contrast shows the missed opportunities that health systems and countries are facing because of high prices.

Third, even for those patients who *have* received treatment, the significant budgetary expenditures on a single therapy by health systems have raised questions over how to balance the opportunity costs with spending in other areas of social and health concern (Reinhardt 2015).²⁵² For example, in the year 2015, the Veterans Affairs system, even after receiving discounts, spent 17% of their entire pharmaceutical budget on *sofosbuvir*-based medicines (Graham 2016). In the same year, the state of New York's Medicaid program spent 10% of their drug budget to these medicines as well (Goldberg 2016). Such allocations require drastically raising overall health spending on pharmaceuticals or making challenging fiscal choices in other vital areas of public spending.

In sum, though this innovation process has produced a veritable clinical advance with the potential for major gains in public health, much of this potential has dimmed as the prices of the medicines have led to an uneven deployment and challenging fiscal pressures.

6.3 The limits and uses of dominant economic accounts as justifications

Considering this sociological and political economy analysis, how might we understand the claims made in the dominant economic accounts of risk and value? This section pursues this question by taking the claims made in each account with regards to the hepatitis C and *sofosbuvir* case, and then juxtaposing them against the evidence yielded by the representation of the innovation process I built over the three empirical chapters (and summarized in sections 6.1 and 6.2). Through this juxtaposition, I illustrate the limits of both economic answers in explaining the

²⁵² In discussing the *sofosbuvir*'s costs to public health systems, Reinhardt (2015b) describes the stark tension: "The government has to be mindful of the social opportunity costs of high health care spending, which means beneficial activities such as education and infrastructure are displaced by high spending on health care."

prices of *sofosbuvir*. Yet even in their limitations, I demonstrate their uses in the innovation process: to conserve a distribution of capital between shareholders, speculative actors, and the state as a given, naturalized order. To conclude this section, I show how my diagnosis of financialization has provided analytical gains not possible with the monopoly-state critique of drug prices.

6.3.1 Risk and risk-mitigation

Under the risk argument, patent protected pricing power is argued to be necessary due to the failure-ridden, long-term nature of drug development. As I described in chapter 1, this link can be formally represented with this simple equation:

$$P = C + I$$

where C = cost of research and development and I = profits

We see the limits of this purported relationship between price and cost with a brief review of the relevant numbers in the *sofosbuvir* innovation process. Pharmasset's reported expenses for developing sofosbuvir into Phase II clinical trials were \$62.4 million, and their total expenses for *all* research and development, including failed compounds and dead-end research, amounted to \$281 million between 2001-2011. Yet Gilead's \$11 billion acquisition cost for Pharmasset represented a sizable difference with Pharmasset's research and development costs (39 - 171x). Gilead later reported spending \$880 million on running late-stage clinical trials on *sofosbuvir* and *sofosbuvir*-based combinations with their internally developed compounds. During the years of these clinical trials (2012-2013), Gilead spent a total of \$4.02 billion in research and development across all areas (see Table 6.1) (Gilead Sciences 2017). But the revenues generated by Gilead's end-stage pricing (\$45 billion over three years) will only increase in multiple over its costs of research and development as they continue to accrue revenue in future years. In comparing these costs on one side and rewards on the other hand, *we see how little the $P = C + I$ relationship explains in the sofosbuvir case* other than to point out that the rewards were many multiples above costs of development for both Pharmasset and Gilead.

Table 6.3 R&D costs versus financial returns for Pharmasset and Gilead

	Sofosbuvir-specific costs / Total costs including failures during period of sofosbuvir development	Financial reward	Multiple range (Financial reward / R&D costs) ²⁵³
Pharmasset	\$62.4 million / \$281 million (2001-2011)	\$11 billion (acquisition payment by Gilead)	39X - 171X (11/.281; 11/.0624)
Gilead	\$942.4 million / \$4.02 billion (2012 - 2013)	\$45 billion (revenues to Gilead from <i>sofosbuvir</i> -based medicines, 2014-2016)	11X - 47X (45/4.02; 45/.942)

Others have noted this disconnect between prices, revenues, and research and development costs (Kesselheim et al. 2016). The industrial economist Scherer (2004) provided an important though limited clarification in a major policy brief in the *New England Journal of Medicine* over a decade earlier: in his view, patent protected pricing was not about *recuperating* costs of risky research and development, but rather served as a *lure* for capital. Just as we observed with Gilead's pricing of *sofosbuvir*, research and development spending figured nowhere into the final calculation and were viewed as sunk costs. What Scherer did not observe however, was that the capital lured into the innovation process through patents was not the 'internal capital of organizations', as is commonly imagined in analyzes of drug pricing and development, but rather the external capital along a chain of speculation within financial markets of intangible assets.

The 'risk' argument is thus plagued by two central limitations: 1) risk is reduced to that of a single actor – the manufacturer – rather than accounting for it across a collective innovation process, and 2) the relationship between patents (which this risk argument attempts to legitimate) and the valuation and pricing logics of financial markets and patents is made invisible. First, as we observed, financial markets offered a way for investors and traders to enter and exit ownership of Pharmasset within short time-horizons and pass risk along to another ownership with the potential for a reward long before the approval of a compound. In other words, multiple financial actors operating across the innovation process, enabled by financial markets, engaged in a process of *risk-mitigation*.

²⁵³ I calculated a multiple range to show how the rewards compared not only to the costs of *sofosbuvir*'s development, but the costs of *all* research and development undertaken (which includes *sofosbuvir*) to give a high and a low range. Even the 'low' range, which uses the costs of all research and development as a denominator illustrates the disconnect between the costs of research and development and accrued rewards.

Second, far from creating and protecting monopolies which finance research and development, patents are instead affixed to the valuation logics and expectations of a chain of financial actors. As we witnessed along the development process for *sofosbuvir*, the mobilization of speculative capital was sustained by an expanding market valuation underpinned by the pricing escalator with investors anticipating buyers paying higher prices for better clinical outcomes. By the time we arrived at Gilead's pricing for *sofosbuvir*, the buyers – public health systems – were many financial exchanges removed from the original and multiple inventors involved in producing the compound.

In this way, claims to patents, legitimated by the 'risk' argument, are severed from their original meaning of a fair exchange between inventors (looking to invest in research and development) and the public (Biagioli 2006; Peterson 2014). Instead, patents – and the intangible assets they secure through legal contracts – buttress the speculative and extractive pursuits of financial actors. As this earlier risk-price relationship is increasingly overwhelmed by these speculative and shareholder-driven dynamics, a second logic has been used to justify prices: the value they deliver to society and health systems.

6.3.2 Value and value-shifting

The second logic used in the dominant economic account is that health systems should pay more for the 'value' of better health outcomes. This value-based pricing is conceived by comparing the medicine to be priced with the existing standard of care and estimating the difference in value that the public (via health systems) will be willing to pay (Gregson et al. 2005). This pricing logic is represented as such:

$$\text{Price} = \text{Value} = R \pm D$$

Where R = reference price, D = differential value estimation

As I described in chapter 5, Gilead's pricing strategy did indeed hold to this composition, as they used the pricing of the existing standard of care at the time (*telaprevir* and *interferon*) to set their reference price for comparison, and estimated that health systems would be willing to pay around the same or a few thousand above the *telaprevir* price because *sofosbuvir*-based regimens yielded improved outcomes. This shaped their decision to charge a \$84,000 launch price for *sofosbuvir* in December, 2013 and \$94,500 for their *sofosbuvir*-based combination that launched less than a year later in October, 2014. A study which tracked hepatitis C drug pricing from the late 1990 interferon regimens onwards to *sofosbuvir*-based treatment found this 'value-

based pricing' strategy to hold across the period, with prices over 15 years of new product launch prices going up \$1,063.68 per each additional percentage increase in cure rate (Vernaz et al. 2016). An array of health economics studies of cost-effectiveness and prevention modelling – which show improved health compared to prior standard of medicine per dollar spent as well as averted downstream medical expenses - has attempted to justify these price increases as 'value-based' (see Appendix D).

Similar to the 'risk' answer, this value logic suffers from the two central limitations: the differentiated and dynamic nature of value is reduced to a single (cost-benefit) metric, and the relationship between value and financial markets is obscured. First, value here is defined narrowly at the point of an exchange between a business and a health system buyer, not tracked in terms of overall flow between multiple sources (value creation) and potential destinations (towards activities that range from sustainable value creation to value extraction). For example, the contribution of an entrepreneurial state in the development of *sofosbuvir* was absented, with the state gaining no direct stake in the assets that public funding helped create (i.e. lack of VA licensing or stake in Pharmasset) and only diminished benefit back from the revenue on those assets (i.e. Gilead's offshoring of *sofosbuvir*'s intellectual property for tax avoidance purposes and prices creating fiscal and treatment access pressures for public systems). Furthermore, much of the value exchanged in transactions between Gilead and public health systems was ultimately stockpiled for future acquisitions and directed to Gilead's shareholders through buybacks and dividends. The health policy scholar Uwe Reinhardt has called this phenomenon in pharmaceuticals *value-shifting*, in that Gilead's shareholders have gained a disproportionate share of the value that has materialized from the development of *sofosbuvir* (Reinhardt 2016). I take this further, arguing that value-shifting occurred in varying degrees across the innovation process – from venture capitalists risking capital for a significant gain, to Gilead's shareholders engaging in *value extraction* – taking advantage of their position of control to, as Veblen would put it, 'gain something for nothing'.

Second, the links between this value logic and financial markets are, like with the 'risk' argument, obscured. Each R + D combination formed a pricing escalator that I described earlier, with health economic studies translating this formulation into 'value'. These studies suffered from a methodological fault: as prices rose, along with the number of patients eligible to benefit from improved treatments, value-based pricing failed to consider the impacts of higher aggregate costs on public budgets – which ultimately led to access restrictions and diminished the very health

value being touted for the treatment.²⁵⁴ Furthermore, these studies required *abstracting* health away from patient's lived experience of being infected with hepatitis C – and instead calculated value by imputing quantitative values (i.e. QALYs) that could be aggregated over a patient's life time and across a population.²⁵⁵ My analysis of financialization showed, however, that the R+D underpinning value-based pricing and used in these health economics studies had less to do with valuing health and the experience of patients infected with hepatitis C, but rather more so to do with the mobilization of speculative capitals in financial markets - with investors, traders, and Gilead anticipating rising market valuations for intangible assets (the *pricing escalator*). In this way, 'value-based pricing' methodologies are fundamentally intertwined with the logics of speculative capitals and can be understood to be an artefact of the financial markets in which these capitals circulate.²⁵⁶

6.3.3 The uses of justifications

By revisiting dominant economic accounts on 'risk' and 'value', I demonstrated each of their limitations in explaining the prices of *sofosbuvir*-based medicines. 'Risk' and 'value' were 1) reduced to static metrics rather than considered as dynamic forms across an innovation process as well as 2) abstracted away from the financial market contexts in which biomedical innovation occurred in the case of hepatitis C. But my accounting of the innovation process in chapters 3 through 5 also shows that these economic arguments cannot be merely dismissed. Rather, we can understand both accounts as *central forms of justifications for drug pricing advanced by powerful actors to conserve a given distribution of capital*.²⁵⁷

²⁵⁴ I described this dynamic in chapter 5 (section 5.2) as well as chapter 1 (section 1.1.2).

²⁵⁵ For an extended and rich discussion on how health economics and clinical epidemiology studies today abstract health away from patient's experiences and buttress the business models of pharmaceutical companies, see sociologists Sunder-Rajan's (2017) new book *Pharmocracy*, as well as Joseph Dumit's (2012) book *Drugs for Life*.

²⁵⁶ Peterson's work (2014:138) on speculation in pharmaceutical assets, though in a very different geographic context (Nigeria), is relevant here. She writes, "These politics (of pharmaceutical valuation) are a far cry from Joseph Schumpeter's description of the monopoly as producing a low-risk environment for business innovation [...] The ultimate result is that a politics of valuation is dissociated from the actual health needs of a population and, instead, connected to the speculative dynamics of pharmaceutical markets and industry practices."

²⁵⁷ Here, I draw on Veblen's conception of control in capitalism in relation to societal values, developed later by Nitzan and Bischler (2009) as well as Cochrane (2011). In a piece tracing Veblen's conception, Cochrane (2011:120) argues that "control actually constitutes the *axia* of every non-egalitarian society, with other values serving as an *a posteriori* justification for a distribution that favors the powerful". In this case, I adapt Cochrane's observation to situate 'risk' and 'value' as two forms of justifications – one *ex-ante* and one *ex-post* – that play out in the social spaces in which struggles for the control and distribution of capital in biomedical innovation are at stake.

Both accounts operate as types of justification for drug pricing. ‘Risk’ is used as an *ex-ante* justification by the pharmaceutical industry for patent-protected pricing power: no drug company will do research on a promising lead without intellectual property in place beforehand (Jasanoff 2011). ‘Value’ is used as an *ex-post* justification, with end-stage manufacturers using health economic studies to demonstrate the relative value of their therapies to health systems at the launch prices they have set after a lengthy drug development process (Reinhardt 2015). As I highlighted in chapter 5 as well as my opening literature review, an array of academic, public relations, and lobbying clout – taken up by Gilead Sciences and the industry at large but also used by physicians and policy-makers – has attempted to advance the use of these justifications to legitimate the prices of drugs. At stake with these justifications are two critical features of the innovation process: the *ownership and control* over intangible pharmaceutical assets, closely linked with *laissez-faire pricing regulations* by government health systems. By attempting to use the ‘risk’ and ‘value’ arguments to legitimate these features of ownership and control, these accounts have become ‘internal’ to the innovation process itself: the unwillingness of the US state to exercise its Bayh-Dole ‘march-in’ rights and the limited use of countervailing power by the state with regards to *sofosbuvir* drug pricing were two examples of how the innovation process I described is sustained and reproduced.

Beyond attempting to legitimate drug pricing, these accounts thus also serve another purpose: *to conserve a given distribution of capital in the innovation process*. This given distribution privileges, as I have illustrated in my findings, several actors and dynamics, such as the “maximizing of shareholder value”, the rewarding of venture capital and traders in financial markets to finance biotechnology, and a ‘market-fixing’ state enabling conversion of public science into private intangible assets but otherwise getting out of the way.²⁵⁸ Though the ‘risk’ and ‘value’ accounts do not explicitly refer to this distribution of capital, they help sustain the modes of capital circulation and accumulation critical to the reproduction of these actors and dynamics in the innovation process.

²⁵⁸ An array of scholarship has pointed to the mythologies contained within each of these privileged dynamics, which I have alluded to in varying degrees throughout this dissertation. As a starting point for further insight into the mystifications involved in such economic arguments, see Lynn Stout’s (2013) work on the Myth of Shareholder Value; Nightingale, Martin, and Hopkins’ writings as well as Pisano’s work on the myth of the biotech revolution (Hopkins et al. 2007; Nightingale and Coad 2014; Nightingale and P. Martin 2004) and Pisano’s work on the limits of venture capital (Pisano 2006); Mazzucato’s elaboration of the discourses that obscure our understanding of public-private sector relations (Mazzucato 2013b).

Yet none of these dynamics were a ‘given’ in the unfolding of the innovation process behind *sofosbuvir* – as I have described through my empirical investigation, this distribution of capital has been a *historical and politically contingent configuration* in which the relations of powers between multiple state, business, and financial actors have been continually at stake. Share buybacks, for example, have not always been a dominant capital allocation strategy for pharmaceutical businesses. Making public science into financial assets has not been a trans-historical phenomenon: the Bayh-Dole Act passed by the US Congress in 1980 created the political-legal contract by which this could occur. This contingent nature, highlighted by these two among many other examples, should offer promise to those positing reforms and imagining alternatives: there is no singular, ‘given’ way to configure biomedical innovation. But the uses of justifications, such as the ‘risk’ and ‘value’ arguments, highlights the vital importance for reformers to attend to and dissect the symbolic power of discursive claims in conserving a taken-for-granted distribution of capital. This appeal harkens to Bourdieu’s call at the opening of this chapter: changing the future of biomedical innovation will require entering into social spaces of struggle and re-imagining the very vision and categories by which a distribution of capital is produced and reproduced.

In conclusion, this section has thus sought not only to describe the limits of both economic accounts but also to illustrate the mechanisms by which these accounts have operated within the innovation process as strategies to legitimate drug prices and naturalize a given distribution of capital.

6.3.4 A note on the monopoly-state relationship

The monopoly-state analysis, lacking a consideration of the dynamics constituting financialization that I have described in this dissertation, not only fails to fully explain *sofosbuvir*’s prices, but also cannot mount an effective interrogation into the limits and uses of the dominant economic answers of ‘risk’ and ‘value’ I have thus far outlined in section 6.3.

As I illustrated in chapter 5, Gilead’s monopoly power – with patent protection over *sofosbuvir* – combined with its lobbying clout to set prices at the upward limits of what they estimated public health systems could pay. But this monopoly-state relationship does not alone explain *sofosbuvir*’s prices, as it takes a narrow view of the structure and operation of the ‘monopoly’ in the innovation process. First, the patent protection over *sofosbuvir* was controlled by multiple financial actors before Gilead Sciences, with hepatitis C assets deriving their value

from the anticipation of rising prices and expanding market size. Second, Gilead's monopoly control over *sofosbuvir* was shaped by its relationship with financial markets and shareholders – with the expectation of continued growth structuring Gilead's position as an 'accumulation center' in the innovation process, using capital derived from high priced medicines to acquire late-stage assets and distribute capital to shareholders. Third and finally, Gilead's position with the state was governed not only by the health delivery state, but rather by a multi-valent state operating in different domains of the economy, from entrepreneurial public sector organizations making risk-taking investments to different bodies governing the rules of control over capital.

With out this processual view of innovation, the monopoly-state critique also falls short in contending with the limits and uses of prevailing economic answers. The reduction in research and development investments alongside high prices - or a turn to value-based pricing – are both presented in the monopoly-state critique as the outcome of profit-maximizing businesses and its political power. Yet as I demonstrated above, such a critique remains incomplete with out a consideration of the financial contexts in which profits are not the only concern – but where the anticipation of *growth* structures the ways in which 'risk' and 'value' are dynamically configured and shaped (see my discussion on 'risk-mitigation' and 'value-shifting' above.) With these limitations, such an analysis of the monopoly-state relationship thus also offers narrow prescriptions by locating solutions at the point of exchange between a company and a government health system, such as increasing the negotiating power of the state in drug prices.²⁵⁹ Yet my analysis shows the multiple mechanisms and relations of power that may be levers for attention in addressing the challenges of high drug prices, from alternative sources of funding for clinical trials to limiting (or prohibiting) share buybacks.

I next turn to specifying and extending the contributions that this dissertation offers before reflecting on the limitations I confronted through my research.

6.4 Contributions, Limitations, and Questions for the Future

In describing the three mechanisms underpinning the prices of *sofosbuvir* as a case of a financialized mode of accumulation, taking stock of its outcomes and consequences for both innovation and public health, as well as re-considering the existing answers on the prices of new medicines, I have pursued a set of contributions to the scholarly and policy debate that I highlight

²⁵⁹ A potentially important solution, but only one tool in a broader toolkit.

in this section. Yet the study was also bounded by several limitations; in identifying each of these, I forecast potential directions for further inquiry to complement a rich and growing research agenda into the links between financialization and and biomedical innovation.

6.4.1. Contributions

My dissertation makes three central contributions: a set of novel empirical findings on a crucial case, a synthetic analytical orientation towards studying drug pricing and biomedical innovation, and a methodological strategy bolstered by access to rare sources of data. These contributions in turn point towards a growing platform for scholarship and potential policy interventions.

First, I made a set of novel empirical findings on a crucial case of drug pricing and biomedical innovation by linking the mechanisms of financialization to the prices of *sofosbuvir*-based medicines. While prior analyzes of financialization had alluded to its influence in rising drug prices at a sector-wide level, I used a single case to more precisely illustrate the ways in which market valuations shaped the mobilization of speculative capital and how the control and expectations of shareholders structured Gilead as an accumulation center in the innovation process, distributing capital to shareholders and acquiring late-stage assets to generate further accumulation. I also ‘retrieved’ the role of an entrepreneurial state largely absented in public debate over *sofosbuvir*, while also tracing the role of the US state’s rule-making functions in governing the relative powers of different kinds of capital at play in the innovation process. In describing these mechanisms, I illuminated the dynamics particular to a *curative therapy* under conditions of financialization – with the downward slide to a *patient cliff* reinforcing Gilead’s speculative and extractive strategies in an effort to generate near-term growth for shareholders. With these insights, I was able to counter and situate the dominant economic accounts of risk and value in ways that can provide alternative policy critiques of rationales for high drug prices than those currently at the center of debates. The potential usefulness of these findings has been demonstrated during my dissertation, with three publications offering a slice of these findings – to which Gilead’s senior leadership responded directly in one case – and a meeting with the U.S. Senate Finance committee staff to share my research.²⁶⁰

²⁶⁰ See online for my July 2016 publication in the *BMJ*, Roy and King (2016) and the response by Gregg Alton, Gilead’s Executive Vice President. This publication primarily focused on findings from chapter 5, and my work has evolved since then as I have put together my dissertation.

Second, these empirical findings were linked to my analytical orientation, which drew together disparate literatures in a synthetic manner. This orientation can be used to investigate other cases of biomedical innovation and issues related to pricing and regulation. Rather than taking the existing economic account on hepatitis C and *sofosbuvir* as essential givens, I expanded the frame of analysis by looking at the nexus of *relationships* between state, business, and financial actors in a historical, *processual* manner. Though most sociological approaches of pharmaceuticals have privileged the state-business dyad, this triad of relationships may be used for analytical gains in multiple arenas of investigation in biomedicine and pharmaceuticals. My analytical orientation also highlighted the potential for applying Veblen to studying biomedical innovation and the pharmaceutical sector. His conceptualization of capital as 1) ownership and control over a community's socially produced assets, 2) a quantified and future-oriented form of control aimed at differential growth and accumulation and 3) a relational form of power indicated through the capitalization process – can be a useful way to think about and interrogate the political-economic dynamics of the contemporary drug development process and broader life sciences sector given its place as a knowledge and capital-intensive domain of the economy (Birch 2016, Gagnon 2016).²⁶¹

Third, this analytical orientation animated my pursuit and interpretation of data sources that are typically not mined, such as the interactions between investment analysts and senior executives at large companies on earnings calls. Reviewing earning call transcripts, for example, illuminated the stark dynamics of 'cure markets', the expectations and influences of financial markets, and the configuration of and response to recurrent episodes of crisis that Gilead faced. The release of the U.S. Senate Investigation also offered a surprise at the mid-point of my dissertation. Where most observers did not go beyond the initial 150-page Senate report, my analytical orientation allowed me to go further and interpret the nearly 1,500 pages in appendices on Pharmasset and Gilead's internal operations and strategy. A review of internal corporate documents and board meeting minutes revealed, for example, the orientation of Pharmasset and Gilead to one another prior to the acquisition, and the relations of power at stake in the capitalization and betting process. This data proved critical to building my account of the innovation process. As researchers aim to re-embed analysis of biomedical innovation in the

²⁶¹ This conceptualization allowed me to unpack, for example, the specific valuation logics underpinning Gilead's \$11 billion acquisition of Pharmasset, the structural crisis for larger drug companies created by demands for continual differential growth, as well as the financial market reaction to a curative therapy (an asset with a declining future earnings stream).

social and political-economic contexts in which it occurs (or fails to occur), an array of Congressional reviews and reports into pharmaceutical companies in recent years as well as earnings call transcripts offer two potential sources of data.²⁶²

Taken together, my contributions and findings on financialization point also point to a larger platform of emerging sites of intervention and reinvention to address drug pricing. First, my findings help better situate existing proposals made in the drug pricing debate, which focus on the manufacturer-health system relationship. Second, and perhaps more importantly, my analysis of financialization indicates that the search for solutions must not be limited to a single relationship between manufacturers and buyers, but rather should focus on multiple levers of power across an innovation process that may influence drug prices. These proposals are motivated by a notion that debates over drug prices and access to medicines have a normative, moral dimension, in which health is viewed not as just any asset or public good, but rather a domain for which we may need to imagine a political economy for health as a human right (Orsenigo et al, 2009).

In the first category of potential solutions are the calls for governments and health systems to be able to better negotiate and regulate the prices that manufacturers can set. Across Europe and even now with growing momentum in the U.S., ‘value-based pricing’ is held to be one method for restraining drug prices (Bach and Pearson 2015). But as I described in chapter 5, while ‘value-based pricing’ may provide a ceiling to the charges that company’s may charge, the overall trend towards ever higher prices will be challenging to restrain as each price sets the floor for the next price in a therapeutic area (Bach and Pearson 2015; Sarpatwari et al 2016).²⁶³ Another strategy being considered are laws that mandate ‘transparency’ whereby companies are required to report research and development costs associated with price setting (Sarpatwari et al 2016).²⁶⁴ The main

²⁶² For example, recent Congressional investigations into Turing Pharmaceuticals, Valeant Pharmaceuticals, and inquiry into Mylan Pharmaceuticals all offer opportunities to examine how different companies approached drug pricing from within the corporation (Rockoff et al. 2016).

²⁶³ Value based pricing may give governments a limited tool to regulate the upward increases in price by setting ceilings on the rate of increase, like the NHS has done, above which they are likely to not pay for a new drug (Bach and Pearson 2015). Yet this will not lead to a major shift in the overall dynamics around value creation and value extraction that are at play with financialized innovation, and prices will likely continue to rise well beyond rate of inflation (Reinhardt 2015).

²⁶⁴ Multiple US states are considering legislation requiring companies to report research and development costs when prices of new medicines are set (Sarpatwari 2016). Reporting research and development expenses on a per drug basis, as Pharmasset and Gilead did in the US Senate investigation, can be a political tool via offering transparency, but as I highlighted in chapter 1, still will leave open multiple kinds of

benefit of such a proposal would be political in nature, as it would likely provide greater evidence for the uncoupling of research and development expenses and drug prices. Such evidence may embolden efforts at legislative changes for drug pricing regulation, and in the long-run could provide more data for advocates pushing for alternative models of health innovation. Finally, another direction might be to consider new public-private contracts that allow for fair pricing deliberations in cases where innovation processes receive significant public investment (often well beyond early stage science). This could also include public ownership stakes in companies where the state makes a direct investment, whereby taxpayers receive a return that can be reinvested into nurturing further public investment for innovation (Mazzucato 2016).

The second category I identified above involves looking more at the multiple sites and levers by which financialization operates across innovation processes. One direction is the search for more patient forms of financing (i.e. more patient venture capital, public financing) across the currently fragmented and linear chain of speculative financial actors. The boldest alternative in this direction would be the development of a 'prize system', in which philanthropic and public grants could 'push' research forward, and publicly financed 'prizes' could pull developed products to market (Baker 2008; Love and Hubbard 2009). In this strategy, prizes would replace patents as the reward mechanism, as prices would be coupled to the costs of production, thereby significantly lowering drug prices: entrepreneurial teams would receive prizes as compensation, and generic manufacturers would receive the license to produce the new technology for a marginal profit. Such a strategy may work in an area of major public health concern, such as antibiotic resistance, infectious diseases such as HIV, and cancer. Another direction in this second category aimed at financialization are changes in the rules of corporate governance that privilege shareholders, such as untangling the nexus of ties between executive compensation, shareholder power, and capital distributions via buybacks (Lazonick 2014; Lazonick and Mazzucato 2013). For example, limiting stock-based awards as well as share buybacks could lead to firms relying less on price increases on existing products as well as expensive late-stage acquisitions for generating short-term growth and instead invest more in long-term research and development. This may lead to a 're-coupling' of drug prices more closely with the costs of innovation, with the additional benefit of providing greater capital for the long-term risks required in biomedical research.

interpretations – such as how to account for the speculative costs of acquisitions or even what implication such data has for pricing, given the financialization of drug development.

Table 6.4 below summarizes this survey of potential directions for drug prices, in which prices are ‘coupled’ less to the structure, expectations, and power relations of financial markets and more to alternative metrics, such as public budgets and public investments, as well as the costs of production and innovation. Further research and policy experimentation will yield evidence on the effectiveness of these possible directions. A central lesson offered by this dissertation is that no single lever will address the challenge of drug prices; the survey of levers I offer here is by no means an exhaustive elaboration of policy directions, but points to the wide landscape upon which reformers might imagine solutions given the impacts of financialization.

Table 6.4 Scenarios for coupling prices to production, innovation, and/or public health

Drug prices coupled to:	Main political-economic mechanisms	Consequences for drug prices
Public budgets and public health need	Increasing government negotiating power; value-based pricing assessments	Increases in drug prices may be restrained over time, with governments better able to assure universal coverage for new health technologies
Public investment	State takes ownership stakes in financed companies; public-private contracts developed in which prices negotiated upfront in areas of significant public investment	State gets a direct return on investment through stake while also contracting with private manufacturers to assure access for technologies developed with public investment; drug prices would be related to public investment and also budgets of health system buyers
Cost of production	Prize system where patents are licensed to generic manufacturers in exchange for entrepreneurial teams/companies receiving major financial reward	Prices significantly drop in areas of health research where public prizes are created and new therapeutic development occurs.
Cost of innovation	Reforming/limiting share buybacks and executive compensation; instituting reforms towards more ‘stakeholder’ oriented corporate governance	Companies may invest more in long-term research and couple their prices (and profits) to their re-investments, resulting in a slower rate of growth in prices.
Financialization and what ‘society can bear’	Status quo of stock-market and shareholder-driven model, in which prices and corporate strategy are linked to meeting expectations of near-term growth	Escalating drug prices that are linked to the upward limits of what ‘society can bear’, as in Gilead’s case with <i>sofosbuvir</i>

Note: Gray boxed indicate alternative directions for drug prices.

6.4.2 Limitations and questions for the future

My study was bounded by three limitations. While none of these limitations hampered by ability to answer the two questions set forth, each translates into potential directions to extend research into the mechanisms and outcomes of financialization in relation to biomedical innovation.

First, my analysis looked at a single case, which limits the potential generalizability of the findings (i.e. the extent to which financialization, as defined in this dissertation, plays a role in other therapeutic areas). However, my aim from the beginning was to use the deeper interrogation offered by analysis of a single case to trace the central mechanisms and relations of power at stake, which could inform a larger comparative analysis across compounds and therapeutic areas. For example, comparing the *sofosbuvir* case with the innovation processes behind a particular oncology technology (such as CAR-T) in the present and a process from the past such as anti-retroviral therapies for HIV/AIDS in the 1980s and 1990s may yield comparative historical insight into shifting political-economic and organizational dynamics explaining drug development and pricing. A study could also compare across multiple therapeutic areas contemporaneously to examine the extent to which state-business-finance dynamics differ or are similar by therapeutic type (biologics versus small molecules) or health challenge (i.e. cancer versus HIV/AIDS).

Second, within the category of financial actors, I did not distinguish between different kinds of shareholders when discussing Gilead's owners, besides identifying Gilead's executives as major shareholders themselves in addition to institutional shareholders. While I did follow the differences between speculative capital, venture capital, and corporate capital (Roche), I largely held Gilead's shareholders to be acting as a monolithic group. Part of the reason for this limitation is that I could not reach investors with the top institutional shareholders with links to the hepatitis C case for interviews. My analysis of Gilead's shareholders relied heavily on investor notes and earnings call transcripts, which provided one lens into understanding how financial markets were potentially shaping the company's strategies. Additional research could focus on interviews as well as deeper documentary searches aimed at unveiling the role of other institutional investors such as hedge funds and pension funds. Elucidating the specific function and strategies of these actors can provide further insight into how financial markets fuel valuations and structure the business models of small and large companies.

Third, my account of the state's role in the innovation process, and with regards to financialization specifically, did not fully trace the strategic interests and relations of power that influenced public organizations and state-rule making processes.²⁶⁵ Instead, I focused my attention on the trajectory of intangible assets and the flow of capital allocation, accumulation, and distribution within the *sofosbuvir* innovation process – and then drew on others' historical studies of state policy and regulation to understand their links to the *sofosbuvir* case (i.e. Bayh-Dole Act, Rule 10-b-18, Medicare Part D drug pricing negotiation). This allowed me to answer my research questions into the organizational and political-economic dynamics of *sofosbuvir*'s innovation process and pricing. But unlike the 'thick' account I provided of the entrepreneurial state's role in the *sofosbuvir* innovation process, my treatment of the state's governance pointed to the state's role in permitting and sanctioning certain rules in different domains of the economy without fully tracing the ways in which these rules may have been influenced and changed over time. A fuller account of the state's role in the financialization of biomedical innovation could bring together historical analysis of each of the key policy shifts raised in this dissertation, a political sociology of the relationships *within* the state between different US public sector organizations (such as the NIH, FDA, VA, SEC), as well as a tracing of the relations *between* the state and business and financial actors. One potential direction may be to investigate the relationship between publicly funded science and contracts over future drug pricing.²⁶⁶ A direction of research analyzing the state may take a cue from Gretta Krippner's work in *Capitalizing on Crisis*, in which she traces financialization from the perspective of state policy-makers, and how their attempts to address different crises beginning in the 1970s ultimately led to the rise of finance (Krippner 2011).

These three limitations in my investigation – a focus on a single case, Gilead's shareholders as largely a monolithic group, and a limited tracing of the state's governance with

²⁶⁵ A thorny area for investigation in relation to the state are the uses of publicly funded science across borders as a global public good – as happened in the case of the replicon and the McGuigan method – in which multiple states financed the development of critical inputs to *sofosbuvir*. Such an effort fell outside the scope of the dissertation, but see work by Suerie Moon and colleagues on the potential for a global R&D treaty to address research for vulnerable populations (Moon et al. 2012).

²⁶⁶ The NIH has enabled technology transfer since the 1980s with private companies, but in the mid-1990s struck a 'reasonable price' clause from their agreements (Richtel and Pollack 2016). Though the Bayh-Dole Act stipulates a march-in clause in cases of public health concern such that the US government can license intellectual property, the clause has never been exercised in 37 years (Silverman 2016). Similarly, though the Veterans Affairs finances research and development, they did not take any stake in Schinazi's intellectual property nor the development of Pharmasset. Further research within the state may elaborate potential explanations for these outcomes.

relation to the financialization of biomedical innovation – all can be complemented by existing or emerging threads of scholarship. Such research can further our understanding of political-economic dynamics that have re-configured the way new medicines are developed, valued, and priced.

Conclusion: Back to Extraction and Onwards to Care

In following the trajectory of *sofosbuvir* in this dissertation, my research indicates a kind of return to an earlier time in drug development. The modern pharmaceutical industry's genesis in the 19th century began with isolating therapeutic elements from plants that would ultimately lead to medicines such as aspirin (for its analgesic and anti-fever properties) and chloral hydrate (for sedation). As Hopkins et al (2007) elaborate, a particular 'heuristic' molded the early developers of medicinal compounds: extraction from the natural world. As the next century unfolded and industrial and technological advances were used in pharmaceutical development, new heuristics came to dominate, such as a focus on synthetic organic chemistry through much of the mid-20th century and a turn to biotechnology in the latter two decades.

The case of *sofosbuvir*, however, reveals a reappearance of an earlier, extraction-oriented heuristic. When applied to *sofosbuvir*, however, the heuristic refers to a social phenomenon whereby rather than extraction drawing directly from nature, we observed a *political-economic* form of extraction, characterized by financialization, in part driven by the shareholders of an established, publicly traded pharmaceutical company. Economic justifications of 'risk' and 'value' have attempted to *naturalize* this political-economic form. I have shown, however, that these economic justifications of drug pricing aim to conserve a distribution of capital that is far from given: rather, the financialization of the innovation process and pricing behind *sofosbuvir*-based medicines has been a historically and politically contingent unfolding shaped by shifting relations of power between state, business, and financial actors. Though I have illustrated this dynamic in a single case of *sofosbuvir*, the increasing use of concepts like 'financial toxicity', elaborated by oncologists to describe the medical side effects their patients experience from the anxiety of high drug prices, is an indication of the broader implications at play in this form of extraction: patients feel it in their bodies (Zafar 2015; Zafar and Abernethy 2013).

This dissertation's introductory chapter concluded with a notion that drug prices which place medicine out of reach for patients and populations strikes against our common-sense ideal of care in biomedicine. As a physician-to-be committed to caring for vulnerable communities, this sense hits me palpably. In the case of hepatitis C, hundreds of thousands of patients continue to wait for *sofosbuvir* in the US, and millions more across the world (Edlin 2016; Iyengar et al. 2016). Yet as I also suggested in the introduction, the moral appeal that this ideal provokes in the face of

such outcomes is not enough on its own to provide an analysis of how these outcomes came to be, or what might be done about them. This dissertation was one modest attempt to provide such an analysis. As my findings demonstrate, crossing the breach between the reality of biomedical innovation under conditions of financialization and the ideal of care will involve more than a single step or a straight path. Our attention must turn towards multiple relations of power and flows of capital and knowledge.

In forging this future, sources for aspiration abound: the economist Carlota Perez, for example, has shown that though financialization has emerged in every technological epoch since the dawn of industrial capitalism, the process has also ultimately provoked a societal response in each of these epochs, whereby the technological possibilities of the time are re-balanced towards the concerns of the public, rather than those of financial capital (Perez 2002). If the debate spurred by *sofosbuvir* and the multiple re-imaginings already underway within global agencies, national capitols, and civil society²⁶⁷ are any indication of the early stages of this response, the kind of future where new medicines are put more fully in the service of care is not beyond our sight.

²⁶⁷ See UN High-Level panel on access to medicines from 2015-2016 (<http://www.unsgaccessmeds.org/new-page/>) and report by Universities Allied for Essential Medicines for examples of alternatives currently being explored (Greenberg and Kiddell-Monroe 2016).

Glossary of Key Terms

Scientific and medical terms

Fibrosis – progressive scarring of liver tissue which can lead to cirrhosis, or impairment of liver function; caused by the body's immune response to the hepatitis C virus, among other potential causes; patients with hepatitis C can be 'staged' for the severity of their liver damage using 'fibrosis scores', with 'Fo' indicating earliest stages, and F4 indicating more advanced liver disease.

Interferon – the medicine used in treatments for hepatitis C prior to *sofosbuvir*; highly toxic side effects, long treatment regimen (upwards of 1 year), and cure rates below 50% meant that only sickest patients with hepatitis C typically tried the medicine.

Nucleosides – refers to the class of medicinal compounds which insert themselves into the genetic material of a replicating pathogen, thereby terminating replication. *Sofosbuvir* is one such nucleoside compound, targeting the NS5b polymerase of the hepatitis C virus and thereby inserting itself into hepatitis C genetic material.

Replicon – a pivotal research tool which enabled replication of the hepatitis C genomic material while producing the key viral proteins used as targets in drug development; developed in the late 1990s and early 2000s by US and German scientists and used by drug developers to test compounds directly against the hepatitis C virus to measure anti-viral effect.

Sustained virologic response (SVR) (or cure rate) – the failure to detect virus for 12 weeks after the completion of treatment; used as a surrogate end point in hepatitis C clinical trials and is clinically defined as cure. Long-term studies have shown less than 1% of patients to remit after realizing SVR on treatment.

Sofosbuvir (also *PSI-7977*) – the curative medicine for hepatitis C that is the subject of my dissertation, leading to cure rates of greater than 90-95% in most patient cohorts; used as the backbone compound in combination with other secondary compounds as a single, daily oral pill which eliminates the need for interferon; combination therapies referred to as *sofosbuvir-based* treatments; compound known as *PSI-7977* when developed and controlled by Pharmasset. The brand name for *sofosbuvir* alone is Sovaldi, and in combination is known as Harvoni.

Business and finance terms

Assets (intangible and tangible) - a resource that is controlled by the entity because of past creation or purchase and from which future economic benefits are expected; tangible assets are physical, such as land, vehicles, inventory, equipment, or cash whereas intangible assets are non-monetary assets that are without physical substance, such as knowledge, patents, copyrights.

Capitalization – a valuation method that transforms a potential future earnings stream into a present value based on a discount rate.

Cost of capital – the return expected by those who provide capital for the business such as debt holders or equity investors; investors use it to assess the risk of a company's equity and is calculated by weighting the cost of a company's debt and equity.

Differential rate of growth – expectation of investors for capital in a given investment to create a higher rate of return than a competing vehicle of investment, leading to differential accumulation; indicated by Veblen as a core concern driving capitalists in their ownership and control of assets.

Discount rate – the rate of earnings that must be exceeded to justify an investment; used to calculate the value of future cash flows in terms of present value, based on the idea that money tomorrow is less valuable than money today (time value of money).

Launch prices – the prices set by a pharmaceutical company at the time of drug approval; these prices can be discounted (discount prices) via offering health systems rebates.

Net Present Value – the present value of an investment's expected cash flow minus the costs of making the investment; used by business managers to make investment decisions; a positive NPV for an investment project recommends investment by business managers, whereas a negative NPV points towards the rejection of the given investment.

Rate of profitability – also profit margin: calculated by taking the net income (total revenues minus operational, cost of goods sold, taxes, interest) over the total revenue for a business.

Share buybacks – when a company's senior leadership purchases a company's own shares on public equity markets using the company's capital (cash and/or debt), intending to raise the value of a company's share by boosting earnings per share; allowed after a SEC rule change in 1982.

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Appendix A: Data Sources

In this Appendix, I elaborate on the four key sources of data used in this research project:

- **Documentary sources**
- **Semi-structured interviews**
- **Databases**
- **Observation at meetings**

For semi-structured interviews, databases, and observation at meetings, I name each of the sources. Because documentary sources involved hundreds of pieces of content which are contained in the bibliography and in-text citations, I provide a brief description of how I retrieved them and offer a few examples of the kinds of documents I interpreted. Refer to chapter 2 for complimentary description about my data collection strategy.

Documentary sources

Scientific and medical journals	<ul style="list-style-type: none">• First, to identify the key scientific advances in the history of hepatitis C science and drug development, I used Web of Science and PubMed databases using the search terms “hepatitis C life cycle” and “hepatitis C drug development”.²⁶⁸ I looked at the most cited ‘original research’ articles in conjunction with ‘review articles’ to identify key advances as well as the scientists and organizations involved in these advances.• Second, I searched specific journals I knew to be important in the field from my background as a medical student. For scientific developments, I specifically looked at <i>Science</i> and <i>Hepatology</i> to ensure that my prior broad search did not leave out potentially important papers.²⁶⁹ This specific search yielded multiple biographical, opinion, and journalistic pieces that the Web of Science and PubMed queries missed.• Third, I also searched <i>Journal of American Medical Association (JAMA)</i>, <i>New England Journal of Medicine</i>, <i>Health Affairs</i>, <i>Lancet</i>, and <i>the Annals of Internal Medicine</i>, as these are the five key journals that cover health policy issues. I used the terms “sofosbuvir drug pricing” and “hepatitis C treatment access” to identify articles that allowed me to gain a base-line understanding of the deployment dynamics of the <i>sofosbuvir</i> innovation process.• Fourth, an initial set of articles then led into snowballing, with further articles gathered over the course of the research. <p>Here are examples of key articles that were yielded from this collection.</p> <p>Key examples of articles on scientific and technological developments:</p>
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²⁶⁸ I chose ‘life cycle’ to focus on the early science that elaborated the fundamentals of how the hepatitis C virus reproduces itself, where as ‘drug development’ articles built off this previous work to pursue therapeutics designed to interrupt this reproduction.

²⁶⁹ For example, a writer for *Science*, Jon Cohen, wrote three journalistic pieces on hepatitis C drug development that were not captured by the initial search for scientific articles, but which contained important historical data on the drug development process as well as biographical data on a key publicly funded scientist, Ray Schinazi.

	<ul style="list-style-type: none"> ○ Alter, H. J. 2013. "The Road Not Taken or How I Learned to Love the Liver: a Personal Perspective on Hepatitis History." <i>Hepatology</i> 59(1):4–12. <i>Describes the early NIH stages of hepatitis C research from perspective of Harvey Alter, a leading viral hepatitis scientist for forty years.</i> ○ Cohen, J. 2015. "King of the Pills." <i>Science</i> 348(6235):622–25. <i>Describes the founder of Pharmasset and his early research into drug development.</i> ○ Bartenschlager, R., Rice, and M. J. Sofia. 2016. "Hepatitis C Virus—From Discovery to Cure: the 2016 Lasker-DeBakey Clinical Medical Research Award." <i>JAMA. Scientists describes their development of the replicon as well as the discovery and development of sofosbuvir.</i> ○ Sofia, M. J. et al. 2010. "Discovery of a B-D-2'-Deoxy-2'-A-Fluoro-2'-B-C-Methyluridine Nucleotide Prodrug (PSI-7977) for the Treatment of Hepatitis C Virus." <i>Journal of Medicinal Chemistry</i> 53(19):7202–18. <i>Michael Sofia – 'inventor' of sofosbuvir – describes the development process for sofosbuvir.</i> <p>Example of key policy and treatment access articles:</p> <ul style="list-style-type: none"> ○ Brennan, T. and W. Shrank. 2014. "New Expensive Treatments for Hepatitis C Infection." <i>JAMA</i> 312(6):593–94. <i>Interprets Gilead's pricing and implications for insurance and coverage.</i> ○ Van Nuys, K. et al. 2015. "Broad Hepatitis C Treatment Scenarios Return Substantial Health Gains, but Capacity Is a Concern." <i>Health Affairs</i> 34(10):1666–74. <i>Describes downstream health savings from sofosbuvir using epidemiological modeling.</i> ○ Chahal, H. S. et al. 2016. "Cost-Effectiveness of Early Treatment of Hepatitis C Virus Genotype 1 by Stage of Liver Fibrosis in a US Treatment-Naïve Population." <i>JAMA Internal Medicine</i> 176(1):65–73. <i>Describes cost-effectiveness evaluation for sofosbuvir from health economics vantage.</i> ○ Canary, L. A., R. M. Klevens, and S. D. Holmberg. 2015. "Limited Access to New Hepatitis C Virus Treatment Under State Medicaid Programs." <i>Annals of Internal Medicine</i> 163(3):226–28. <i>Describing the extent of treatment access restrictions across the US from 2014-2015.</i>
Media accounts	<ul style="list-style-type: none"> ○ I used Lexis Nexis to search in New York Times, Bloomberg News, Wall Street Journal, and Financial Times between January 1, 2000 to October 1, 2014. I did a more recent search from October 2, 2014 – December 1, 2016 to include major updates. ○ I also followed STAT Health and FiercePharma/FierceBiotech, two websites focused on industry-related news, to stay up to date on further development, which often pointed me to one of the news outlets in the prior bullet.

Organizational and institutional reports and filings	<ul style="list-style-type: none"> ○ US Senate Finance Committee Investigation into Sovaldi's impacts on US health care system, Dec 2015; 2,000 pages, including internal corporate documents from Gilead and Pharmasset ○ NIH – U.S. government documents (8): 2003, 2004, 2005, 2006 – NIH Action Plan for Liver Disease Research launched in 2003, with 3 annual follow-up updates (2004-2006); 1999, 2002 – NIH Consensus Statements on Hepatitis C; December 14, 2004 – testimony to U.S. House Committee on Government Reform by Dr. Jay Hoofnagle, Director of Liver Disease Research Branch of National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) of NIH ○ Annual SEC filings of Pharmasset and Gilead (16): Pharmasset's 10-K annual filings, 2007-2011; Gilead's 10-K annual filings, 2007-2016; Schedule 14D-9; filing of acquisition of Pharmasset by Gilead ○ Investment analyst call transcripts (18): Gilead – Pharmasset M&A Call, November 21, 2011; Gilead's quarterly earnings calls between February, 2012 (first call post-acquisition) and September, 2016 ○ Investor notes and reports (11): RBC Capital (1), Evercore ISI (7), JP Morgan (3) from Thomson Reuters database at Judge Business School ○ FDA-review (4): FDA antiviral drugs advisory committee meeting; background package, GS-7977 (sofosbuvir), October 25, 2013; Gilead Sciences, Antiviral Drugs Advisory Committee (AVDAC) Meeting, briefing document, October 25, 2013; FDA introductory remarks, October 25, 2013, Dr. Debra Birnkrant (slides); FDA, Center for Drug Evaluation and Research, summary minutes of AVDAC meeting, October 25, 2013.
Historical research	<p>I used my literature review, presented in chapter 1 (section 1.3) as an initial starting point from which to identify key papers (and book chapters) that provided historical context on the key rules, policies and political-economic dynamics shaping the <i>sofosbuvir</i> innovation process. From this starting point, I used bibliographies to develop a snow-ball samples of key papers, typically finding atleast 2-3 papers on each domain or area, from Bayh-Dole to the rise of finance. Here is a sampling of the historical research from which I drew insights:</p> <ul style="list-style-type: none"> • Gompers, Paul A. 1994. "The Rise and Fall of Venture Capital." <i>Business and Economic History</i> 23(2). • Keller, M R. and F Block. 2013. "Explaining the Transformation in the US Innovation System: the Impact of a Small Government Program." <i>Socio-Economic Review</i> 11(4):629–56. • Lazonick, W. 2015. <i>Stock Buybacks: From Retain-and Reinvest to Downsize-and-Distribute</i>. Brookings Institution. • Davis, Gerald. 2009. <i>Managed by Markets: How Finance Reshaped America</i>. Oxford University Press. • Kesselheim, Aaron S. 2011. "An Empirical Review of Major Legislation Affecting Drug Development: Past Experiences, Effects, and Unintended Consequences." <i>The Milbank Quarterly</i> 89(3):450–502. • Boettiger, Sara and Alan B. Bennett. 2006. "Bayh-Dole: if We Knew Then What We Know Now." <i>Nature Biotechnology</i> 24(3):320–23. • Rai, Arti and Rebecca Eisenberg. 2003. "Bayh-Dole Reform and the Progress of Biomedicine." <i>American Scientist</i> 91(1):52. • Lazonick, W and M Mazzucato. 2013. "The Risk-Reward Nexus in the Innovation-Inequality Relationship: Who Takes the Risks? Who Gets the Rewards?." <i>Industrial and Corporate Change</i> 22(4):1093–1128.

	<ul style="list-style-type: none"> Vallas, Paul, Daniel L. Kleinman, and Dina Biscotti. 2011. "Political Structures and the Making of U.S. Biotechnology." in <i>State of Innovation The U.S. Governments Role in Technology Development</i>, edited by F. Block and M. R. Keller. Boulder, CO.
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Semi-structured interviews

#	Actor type	Position title	Date	Length (total)	Method
1	pharma business executive	Director, Regulatory Affairs	9/8/2014	60	In-person
2	drug pricing activist	Executive Director of lobbying group	8/24/2014	60	In person
3	pharma business executive	Medical Director	3/4/2015	40	Phone
4	journalist	biotechnology reporter	3/24/2015	40	Phone
5,3 8	pharma business executive	Senior Vice President of Clinical Research	3/27/2015, 7/15/2015	80	phone, In-person
6	hepatitis C clinician	consultant hepatologist	12/3/2014	20	In-person
7	academic scientist	researcher at university lab	2/5/2015	45	Phone
8	public official	CEO of publicly funded insurance group	3/19/2015	40	Phone
9	academic scientist	doctoral researcher	3/19/2015	40	In-person
10	patient advocate/activist	director of legal program	4/13/2015	35	phone
11	pharma business executive	pricing consultant	4/21/2015	20	In-person
12	investment analyst	analyst at major biotech investment group	5/20/2015	60	Phone
13	pharma business executive	CEO of small biotech company	4/9/2015	40	Phone
14	academic scientist	researcher at university lab	5/9/2015	40	phone, email
15	investment analyst	analyst at major biotech investment group	5/23/2015	60	Phone
16	public official	Executive Director of publicly funded insurance group	5/25/2015	60	In-person
17	academic scientist	senior researcher at research institute	5/25/2015	90	In-person
18, 39	hepatitis C clinician	doctor and program director	6/3/2015, 7/22/2015	90	phone, In-person

19	drug pricing activist	access to medicines program director at consumer group	6/5/2015	60	In-person
20	academic scientist	senior researcher at research institute	6/10/2015	40	In-person
21, 40	patient advocate	access to medicines program director at major foundation	6/12/2015, 12/15/2015	60	In-person
22	patient advocate	Executive Director of major patient group for hepatitis C	7/8/2015	60	In-person
23	academic scientist	senior researcher at research institute	7/7/2015	40	Phone
24	pharma business executive	Director, Public Policy	7/20/2015	50	In-person
25	public official	Health Policy director of US Senate legislator	7/27/2015	40	In-person
26	pharma business executive / scientist	Project Manager, lead at major pharmaceutical company	7/30/2015	40	Phone
27	patient advocate	hepatitis C director at patient advocacy group	8/5/2015	40	Phone
28	academic scientist, pharma business executive	organic chemist, CEO of small biotech company	8/15/2015	35	Phone
29	public official	Health Policy director of US Senate legislator	10/22/2015	30	Phone
30	public official	public health expert	12/9/2015	30	In-person
31	pharma business executive	medical director at biotechnology company	12/8/2015	60	In-person
32	academic scientist	senior researcher at research institute	12/8/2015	30	In-person
33	academic scientist	researcher at university lab	12/9/2015	60	In-person
34	medicinal chemist	scientist and executive at small biotechnology company	12/8/2015	40	In-person
35	pharma business executive / scientist	scientist at small biotechnology company	12/10/2015	45	In-person
36	patient advocate/activist	lawyer for access to medicines group	12/15/2015	60	In-person
37	pharma business executive	market analyst for consulting group to large pharmaceutical companies	12/15/2015	20	In-person

41	Venture capitalist	Lead partner at venture fund that invests in biotechnology companies	2/17/2017	60	In-person
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Databases

- **S&P Capital database**
 - Gilead Sciences corporate profile and timeline of all events with all major press releases on product announcements, investor reports along with complete reported financial data
 - Pharmasset corporate profile and timeline of all events with all major press releases on product announcements, investor reports along with complete reported financial data
 - Access provided via University of Cambridge Judge Business School
- **National Institutes of Health database**
 - Reporter database to track public funding for APATH LLC, Pharmasset, Dr. Ray Schinazi, Dr. Charlie Rice
- **Wayback Machine database**
 - Examining archived websites for Pharmasset and APATH LLC
- **Centers for Medicare and Medicaid drug spending database**
 - Collection of data regarding public spending in the US, which includes hepatitis C and *sofosbuvir*-based medicines.
- **OpenSecrets**
 - Political lobbying spending database, which I used to track Gilead's lobbying spending to understand their strategy to influence the US state with regards to their hepatitis C drug prices

Observation of public meetings

Direct observation (6)

Event; Date; Location	Key attendees
FDA/CMS Summit; December 12, 2014; Washington D.C.	A gathering of regulatory officials from the FDA, payers such as the Centers for Medicaid and Medicare, and pharmaceutical companies; notable, John McHutchison, EVP of Clinical Research for Gilead and leading hepatologist and clinical researcher.
British Association for Study of the Liver (BASL) clinicians meeting; March 3, 2015; London	A gathering of leading hepatologists in the UK to discuss Hepatitis C guidelines to be shared with the NHS for upcoming policy development; leading British hepatologist Dr. Graham Foster, chaired the meeting; also notable: Charles Gore, head of the World Hepatitis Alliance, a patient advocacy group, also participated.
Meeting of British Viral Hepatitis Group; March 6, 2016; London	A conference of the BVHG to discuss Hepatitis C strategy with a broader group of hepatologists from across the UK; notable speaker: Dr. Ustianowski, member of NHS Clinical Reference group charged with Hepatitis C policy development as well as

	representatives from each of the major pharma companies with Hepatitis C treatments
National Viral Hepatitis Roundtable World Hepatitis Day meeting; July 29, 2015; Washington, D.C.	A gathering of 25+ key stakeholders involved in Hepatitis C policy; notable: Dr. John Ward, head of Viral Hepatitis department at CDC, industry officials from all major hep C manufacturers
LSE-ICL Forum on Medical Innovation; October 14, 2015; London	A forum between scholars of the pharmaceutical industry sponsored by Gilead Sciences; notable speaker: John Milligan, President and COO, Gilead.
HEPDART; December 6-10, 2015; Hawaii	A forum organized by Dr. Ray Schinazi, leading anti-viral researcher and founder of Pharmasset which ultimately produced sofosbuvir; scientists, pharmaceutical companies, and investors all present at this exclusive meeting forecasting the future of Hepatitis C science and research

Observed online video and/or transcript of event (3)

Event; date; location	Key attendees
If You Cure It, Will They Pay? Placing a Value on Lives?; April 30, 2014; Milken Institute; Santa Monica, CA; (Available at: http://www.milkeninstitute.org/events/conferences/global-conference/2014/panel-detail/4876)	A panel discussion featuring: Gregg Alton, Executive Vice President, Corporate and Medical Affairs, Gilead Sciences, Inc.; Shamiram Feinglass, Founder and CEO, The Feinglass Group; Former Vice President, Global Medical and Regulatory Affairs, Zimmer; Dean Rosen, President and CEO, Breakaway Policy Strategies; Partner, Mehlmán Vogel Castagnetti; Reed Tuckson, Managing Director, Tuckson Health Connections; Sean Tunis, President and CEO, Center for Medical Technology Policy
American Enterprise Institute panel discussion, “How will we pay for cures?”; July 11 th , 2014; Washington D.C. (complete transcript)	Featuring: Gregg Alton, EVP of Corporate and Medical Affairs, Gilead Sciences; Mark B. McClellan, Brookings Institution; Dan Mendelson, Avalre Health; Dirk Calcoen; Boston Consulting Group; Scott Gottlieb AEI; Rep Michael C. Burgess (R-TX)
Brookings Institute panel discussion “The Cost and Value of Biomedical Innovation – Implications for Health Policy”; October 1, 2014; Washington D.C. (available at: http://www.brookings.edu/events/2014/10/01-cost-and-value-biomedical-innovation-hep-c)	Featuring: John Milligan, President and COO, Gilead; Ryan Clary, Executive Director, National Viral Hepatitis Roundtable; Sam Nussbaum, EVP, Clinical Health Policy and Chief Medical Officer, WellPoint; Darius Lakdawalla, Quintiles Chair in Pharmaceutical Development and Regulatory Innovation, USC Schaeffer Center for Health Policy and Economics

Appendix B: NIH Funding for Replicon and Sofosbuvir Development

1. Development of the replicon by Rice Lab
2. Commercialization of the replicon by Apath (led by Rice team)
3. Development of nucleoside science by Schinazi lab
4. Commercialization of nucleosides by Pharmasset (founded by Schinazi)
5. Clinical trials for *sofosbuvir*

Major development	Hepatitis C-specific funding	Overall total grants
Development of the replicon by Rice Lab	\$3.40 million	\$10.76 million (1993-2005)
Commercialization of the replicon by Apath	\$1.81 million	\$9.39 million (2002-2008)
Development of nucleoside science by Schinazi lab	\$2.72 million	\$8.84 million (1992 – 2011)
Commercialization of nucleosides by Pharmasset	\$1.01 million	\$2.46 million (1999 – 2004)
Clinical trials for <i>sofosbuvir</i>	\$.244 million (known grant) ~14.2 million for Phase II trial	\$.244 million (known grant) ~14.2 million for Phase II trial
TOTALS	\$9.18 million in grants Adding estimated cost of Phase II trial = \$23.4 million	\$31.70 million in grants Adding estimated cost of Phase II trial = \$45.90 million

All the grants are listed below by ‘major development’

Replicon development grants

Project Title	Contact PI / Project Leader	Organization Name	FY	FY Total Cost
HCV INFECTION SYSTEMS AND ROLE OF NEUTRALIZING ANTIBODIES IN HEPATITIS C	RICE, CHARLES M.	ROCKEFELLER UNIVERSITY	2005	\$251,675
ADMINISTRATIVE CORE	RICE, CHARLES M.	ROCKEFELLER UNIVERSITY	2005	\$61,004
HEPATITIS C: STUDIES OF IMMUNITY AND PATHOGENESIS	RICE, CHARLES M.	ROCKEFELLER UNIVERSITY	2005	\$848,905
HEPATITIS C: STUDIES OF IMMUNITY AND PATHOGENESIS	RICE, CHARLES M.	ROCKEFELLER UNIVERSITY	2004	\$777,103
HEPATITIS C: STUDIES OF IMMUNITY AND PATHOGENESIS	RICE, CHARLES M.	ROCKEFELLER UNIVERSITY	2003	\$759,817
HEPATITIS C: STUDIES OF IMMUNITY AND PATHOGENESIS	RICE, CHARLES M.	ROCKEFELLER UNIVERSITY	2002	\$701,031
HEPATITIS C: STUDIES OF IMMUNITY AND PATHOGENESIS	RICE, CHARLES M.	ROCKEFELLER UNIVERSITY	2000	\$680,907
CONSTRUCTION AND IDENTIFICATION OF FUNCTIONAL HEPATITIS C VIRUS CDNA CLONES	RICE, CHARLES M.	STANFORD UNIVERSITY	1999	\$236,243

CONSTRUCTION AND IDENTIFICATION OF FUNCTIONAL HEPATITIS C VIRUS CDNA CLONES	RICE, CHARLES M.	STANFORD UNIVERSITY	1998	\$236,243
CONSTRUCTION AND IDENTIFICATION OF FUNCTIONAL HEPATITIS C VIRUS CDNA CLONES	RICE, CHARLES M.	STANFORD UNIVERSITY	1997	\$283,752
HEPATITIS C VIRUS-DEVELOPING ANTIVIRALS AND VACCINES	RICE, CHARLES M.	ROCKEFELLER UNIVERSITY	2005	\$396,857
HEPATITIS C VIRUS-DEVELOPING ANTIVIRALS AND VACCINES	RICE, CHARLES M.	ROCKEFELLER UNIVERSITY	2004	\$395,975
HEPATITIS C VIRUS-DEVELOPING ANTIVIRALS AND VACCINES	RICE, CHARLES M.	ROCKEFELLER UNIVERSITY	2003	\$385,488
HEPATITIS C VIRUS --DEVELOPING ANTIVIRALS AND VACCINES	RICE, CHARLES M.	ROCKEFELLER UNIVERSITY	2000	\$63,500
HEPATITIS C VIRUS --DEVELOPING ANTIVIRALS AND VACCINES	RICE, CHARLES M.	WASHINGTON UNIVERSITY	2000	\$262,940
HEPATITIS C VIRUS --DEVELOPING ANTIVIRALS AND VACCINES	RICE, CHARLES M.	WASHINGTON UNIVERSITY	1999	\$314,595
HEPATITIS C VIRUS --DEVELOPING ANTIVIRALS AND VACCINES	RICE, CHARLES M.	WASHINGTON UNIVERSITY	1998	\$303,203
HEPATITIS C VIRUS --DEVELOPING ANTIVIRALS AND VACCINES	RICE, CHARLES M.	WASHINGTON UNIVERSITY	1997	\$323,448
HEPATITIS C VIRUS --DEVELOPING ANTIVIRALS AND VACCINES	RICE, CHARLES M.	WASHINGTON UNIVERSITY	1996	\$270,224
HEPATITIS C VIRUS--DEVELOPING ANTIVIRALS AND VACCINE	RICE, CHARLES M.	WASHINGTON UNIVERSITY	1995	\$297,719
HEPATITIS C VIRUS--DEVELOPING ANTIVIRALS AND VACCINE	RICE, CHARLES M.	WASHINGTON UNIVERSITY	1994	\$278,900
HEPATITIS C VIRUS--DEVELOPING ANTIVIRALS AND VACCINE	RICE, CHARLES M.	WASHINGTON UNIVERSITY	1993	\$273,694
IMMUNOTHERAPY PROTECTION & VACCINES FOR HEPATITIS C	RICE, CHARLES M.	ROCKEFELLER UNIVERSITY	2003	\$405,730
IMMUNOTHERAPY PROTECTION & VACCINES FOR HEPATITIS C	RICE, CHARLES M.	ROCKEFELLER UNIVERSITY	2002	\$394,651
IMMUNOTHERAPY PROTECTION & VACCINES FOR HEPATITIS C	RICE, CHARLES M.	ROCKEFELLER UNIVERSITY	2001	\$383,896
IMMUNOTHERAPY PROTECTION & VACCINES FOR HEPATITIS C	RICE, CHARLES M.	ROCKEFELLER UNIVERSITY	2000	\$219,764
IMMUNOTHERAPY PROTECTION AND VACCINES FOR HEPATITIS C	RICE, CHARLES M.	WASHINGTON UNIVERSITY	1999	\$453,879
SMALL MOLECULES AS RESEARCH TOOLS FOR HCV BIOLOGY	RICE, CHARLES M.	ROCKEFELLER UNIVERSITY	2004	\$252,750
SMALL MOLECULES AS RESEARCH TOOLS FOR HCV BIOLOGY	RICE, CHARLES M.	ROCKEFELLER UNIVERSITY	2003	\$252,188
			TOTAL	\$10,766,081
			REPLICON	\$3,404,521

Replicon commercialization with APATH: NIH SBIR grants

Project Title	Contact PI / Project Leader	Organization Name	FY	FY Total Cost
DEVELOPING SMALL MOLECULE THERAPEUTICS FOR WEST NILE VIRUS	BEATTIE, JODI	APATH, LLC	2008	\$712,161
DEVELOPING SMALL MOLECULE THERAPEUTICS FOR WEST NILE VIRUS	BEATTIE, JODI	APATH, LLC	2007	\$725,606
THE IN VITRO HEPATITIS C VIRUS INFECTION SYSTEM AS A DRUG DISCOVERY TOOL	NOUEIRY, AMINE OSMAN	APATH, LLC	2007	\$100,713
HEPATITIS C VIRUS RNA QUANTITATION USING THE 3'NTR	OLIVO, PAUL DAVID	APATH, LLC	2002	\$371,356
HEPATITIS C VIRUS RNA QUANTITATION USING THE 3'NTR	OLIVO, PAUL DAVID	APATH, LLC	2001	\$378,638
HEPATITIS C VIRUS RNA QUANTITATION USING THE 3' NTR	OLIVO, PAUL DAVID	APATH, LLC	1999	\$109,410

SCREENING FOR ANTI-RSV COMPOUNDS WITH INDICATOR CELLS	OLIVO, PAUL DAVID	APATH, LLC	2004	\$359,466
SCREENING FOR ANTI-RSV COMPOUNDS WITH INDICATOR CELLS	OLIVO, PAUL DAVID	APATH, LLC	2003	\$411,213
CELLS FOR DETECTING NEGATIVE-STRAND RNA VIRUSES	OLIVO, PAUL DAVID	APATH, LLC	2000	\$99,240
ANTIVIRAL SCREENING ASSAYS BASED ON HCV REPLICONS	OLIVO, PAUL DAVID	APATH, LLC	2003	\$320,675
ANTIVIRAL SCREENING ASSAYS BASED ON HCV REPLICONS	OLIVO, PAUL DAVID	APATH, LLC	2002	\$429,325
ANTIVIRAL SCREENING ASSAYS BASED ON HCV REPLICONS	OLIVO, PAUL DAVID	APATH, LLC	2001	\$99,395
ANTIVIRAL SCREENING AGAINST MULTIPLE VIRUSES	OLIVO, PAUL DAVID	APATH, LLC	2002	\$100,000
INDICATOR CELLS FOR ANTIVIRAL SCREENING FOR FILOVIRUSES	OLIVO, PAUL DAVID	APATH, LLC	2005	\$368,309
INDICATOR CELLS FOR ANTIVIRAL SCREENING FOR FILOVIRUSES	OLIVO, PAUL DAVID	APATH, LLC	2004	\$357,582
INDICATOR CELLS FOR ANTIVIRAL SCREENING FOR FILOVIRUSES	OLIVO, PAUL DAVID	APATH, LLC	2002	\$100,000
SCREENING FOR ANTIVIRALS AGAINST FLAVIVIRUSES	OLIVO, PAUL DAVID	APATH, LLC	2003	\$209,250
SCREENING FOR ANTIVIRALS AGAINST FLAVIVIRUSES	OLIVO, PAUL DAVID	APATH, LLC	2002	\$187,500
CONSTRUCTION OF A RESPIRATORY SYNCYTIAL VIRUS REPLICON	OLIVO, PAUL DAVID	APATH, LLC	2003	\$100,000
MULTIPLEXED GENE ASSAYS BY MICROTITER PLATE MICROARRAYS	OLIVO, PAUL DAVID	APATH, LLC	2003	\$111,600
MOLECULAR TOOLS FOR BUNYAVIRUS ANTIVIRAL SCREENING	OLIVO, PAUL DAVID	APATH, LLC	2005	\$413,699
MOLECULAR TOOLS FOR BUNYAVIRUS ANTIVIRAL SCREENING	OLIVO, PAUL DAVID	APATH, LLC	2004	\$327,339
TRANSGENIC INDICATOR CELLS FOR INFLUENZA VIRUS	OLIVO, PAUL DAVID	APATH, LLC	2006	\$272,949
TRANSGENIC INDICATOR CELLS FOR INFLUENZA VIRUS	OLIVO, PAUL DAVID	APATH, LLC	2005	\$308,949
TRANSGENIC INDICATOR CELLS FOR INFLUENZA VIRUS	OLIVO, PAUL DAVID	APATH, LLC	2004	\$106,026
REPLICON-BASED SCREENING FOR INHIBITORS OF ALPHAVIRUSES	OLIVO, PAUL DAVID	APATH, LLC	2005	\$475,049
REPLICON-BASED SCREENING FOR INHIBITORS OF ALPHAVIRUSES	OLIVO, PAUL DAVID	APATH, LLC	2004	\$483,532
THERAPEUTICS FOR EBOLA VIRUS	OLIVO, PAUL DAVID	APATH, LLC	2005	\$1,350,000
TOTAL				\$9,388,982
Replicon				\$1,809,512

NIH grants for Schinazi-led nucleoside research

Project Title	Project Leader	Organization Name	FISCAL YEAR	Total Cost
CORE--BIOLOGICAL CORE	SCHINAZI, RAYMOND	GEORGIA STATE UNIVERSITY	1992	
BORON-CONTAINING NUCLEOSIDES FOR NEUTRON CAPTURE THERAPY	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	1992	\$133,846
BORON-CONTAINING NUCLEOSIDES FOR NEUTRON CAPTURE THERAPY	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	1993	\$135,579
CORE--BIOLOGICAL CORE	SCHINAZI, RAYMOND	GEORGIA STATE UNIVERSITY	1993	
IN VITRO TEST SYSTEMS FOR COMBINED CHEMOTHERAPIES	SCHINAZI, RAYOND F	EMORY UNIVERSITY	1994	\$265,601

BORON-CONTAINING NUCLEOSIDES FOR NEUTRON CAPTURE THERAPY	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	1994	\$138,180
IN VITRO TEST SYSTEMS FOR COMBINED CHEMOTHERAPIES	SCHINAZI, RAYMOND F.	EMORY UNIVERSITY	1994	
IN VITRO TEST SYSTEMS FOR COMBINED CHEMOTHERAPIES	SCHINAZI, RAYMOND F.	EMORY UNIVERSITY	1995	
BORON-CONTAINING NUCLEOSIDES FOR NEUTRON CAPTURE THERAPY	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	1995	\$146,641
IN VITRO TEST SYSTEMS FOR COMBINED CHEMOTHERAPIES	SCHINAZI, RAYMOND F.	EMORY UNIVERSITY	1996	
ANIMAL MODELS OF HEPATITIS C	SCHINAZI, RAYMOND F.	EMORY UNIVERSITY	1996	\$50,000
SYNTHESIS & BIOTRANSFORMATION OF ANTI HIV PRODRUGS: PHARMACOKINETICS	SCHINAZI, RAYMOND F.	EMORY UNIVERSITY	1997	\$75,504
NUCLEOSIDES WITH DUAL ANTI-HIV AND HBV ACTIVITY	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	1997	\$154,642
CORE--VIROLOGY FACILITY	SCHINAZI, RAYMOND F.	EMORY UNIVERSITY	1998	\$153,440
NUCLEOSIDES WITH DUAL ANTI-HIV AND HBV ACTIVITY	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	1998	\$205,182
CORE--VIROLOGY FACILITY	SCHINAZI, RAYMOND F.	EMORY UNIVERSITY	1999	\$153,440
CORE--VIROLOGY FACILITY	SCHINAZI, RAYMOND F.	EMORY UNIVERSITY	1999	\$153,440
NUCLEOSIDES WITH DUAL ANTI-HIV AND HBV ACTIVITY	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	1999	\$164,061
CORE--VIROLOGY FACILITY	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	2000	\$153,440
NUCLEOSIDES WITH DUAL ANTI-HIV AND HBV ACTIVITY	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	2000	\$192,000
DETERM URACIL IN RHESUS PLASMA; URINE & CEREBROSPINAL FLUID	SCHINAZI, RAYMOND F.	EMORY UNIVERSITY	2000	\$39,712
NUCLEOSIDES WITH DUAL ANTI-HIV AND HBV ACTIVITY	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	2001	\$192,000
NUCLEOSIDES WITH DUAL ANTI-HIV AND HBV ACTIVITY	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	2002	\$194,177
NUCLEOSIDES WITH DUAL ANTI-HIV AND HBV ACTIVITY	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	2002	\$24,884
NUCLEOSIDES WITH DUAL ANTI-HIV AND HBV ACTIVITY	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	2003	\$195,507
SYNTHESIS AND BIOTRANSFORMATION OF ANTI-VIRAL PRODRUGS	SCHINAZI, RAYMOND F.	EMORY UNIVERSITY	2003	\$85,297
SYNTHESIS AND BIOTRANSFORMATION OF ANTI-VIRAL PRODRUGS	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	2004	\$93,006
NUCLEOSIDES WITH DUAL ANTI-HIV AND HBV ACTIVITY	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	2004	\$192,000
NUCLEOSIDES WITH DUAL ANTI-HIV AND HBV ACTIVITY	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	2004	\$72,723
SYNTHESIS AND BIOTRANSFORMATION OF ANTI-VIRAL PRODRUGS	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	2005	\$94,301
HIV DART:FRONTIERS IN DRUG DEVELOPMENT FOR ARV THERAPIES	SCHINAZI, RAYMOND FELIX	INFORMED HORIZONS, LLC	2005	\$16,500
NUCLEOSIDES WITH DUAL ANTI-HIV AND HBV ACTIVITY	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	2005	\$225,925
SYNTHESIS AND BIOTRANSFORMATION OF ANTI-VIRAL PRODRUGS	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	2006	\$107,378

NUCLEOSIDES WITH DUAL ANTI-HIV AND HBV ACTIVITY	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	2006	\$220,615
NUCLEOSIDES WITH DUAL ANTI-HIV AND HBV ACTIVITY	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	2007	\$214,217
SYNTHESIS AND BIOTRANSFORMATION OF ANTI-VIRAL PRODRUGS	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	2007	\$78,544
HIV DART:FRONTIERS IN DRUG DEVELOPMENT FOR ARV THERAPIES	SCHINAZI, RAYMOND FELIX	INFORMED HORIZONS, LLC	2007	\$16,500
SYNTHESIS AND BIOTRANSFORMATION OF ANTI-VIRAL PRODRUGS	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	2008	\$42,758
NUCLEOSIDES WITH DUAL ANTI-HIV AND HBV ACTIVITY	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	2008	\$210,146
VIROLOGY AND DRUG DISCOVERY	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	2008	\$291,198
SYNTHESIS AND BIOTRANSFORMATION OF ANTI-VIRAL PRODRUGS	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	2009	\$68,028
HIV DART:FRONTIERS IN DRUG DEVELOPMENT FOR ARV THERAPIES	SCHINAZI, RAYMOND FELIX	INFORMED HORIZONS, LLC	2009	\$14,850
VIROLOGY AND DRUG DISCOVERY	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	2009	\$336,022
NUCLEOSIDES WITH DUAL ANTI-HIV AND HBV ACTIVITY	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	2009	\$210,146
PRIMATE MODEL TOWARDS HIV ERADICATION STRATEGIES	NORTH, THOMAS W*	UNIVERSITY OF CALIFORNIA AT DAVIS	2009	\$747,943
SYNTHESIS AND BIOTRANSFORMATION OF ANTI-VIRAL PRODRUGS	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	2010	\$65,793
PRIMATE MODEL TOWARDS HIV ERADICATION STRATEGIES	NORTH, THOMAS W*	UNIVERSITY OF CALIFORNIA AT DAVIS	2010	\$713,009
VIROLOGY AND DRUG DISCOVERY	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	2010	\$325,502
PRIMATE MODEL TOWARDS HIV ERADICATION STRATEGIES	NORTH, THOMAS W*	EMORY UNIVERSITY	2011	\$705,879
HIV DART: FRONTIERS IN DRUG DEVELOPMENT FOR ANTIRETROVIRAL THERAPIES	SCHINAZI, RAYMOND FELIX	INFORMED HORIZONS, LLC	2011	\$20,000
VIROLOGY AND DRUG DISCOVERY	SCHINAZI, RAYMOND FELIX	EMORY UNIVERSITY	2011	\$295,726
* Schinazi was co-project leader on these grants.			TOTALS	\$8,385,282
			Viral hepatitis	\$2,718,225

Pharmasset grants from NIH (including SBIR)

PROJECT TITLE	PROJECT LEADER	ORGANIZATION NAME	YEAR	TOTAL
RACIVIR FOR TREATMENT OF HEPATITIS B AND HIV INFECTIONS	OTTO, MICHAEL J	PHARMASSET, INC.	2000	\$142,000
NOVEL COFACTOR ANALOGUES AS IMMUNOSUPPRESSANTS	PANKIEWICZ, KRZYSZTOF W	PHARMASSET, INC.	2000	\$100,001
NOVEL DIFFERENTIATION AGENTS AGAINST HUMAN LEUKEMIAS	PANKIEWICZ, KRZYSZTOF W	PHARMASSET, INC.	2000	\$100,010

L-NUCLEOSIDES AS ANTI-HBV AGENTS	WATANABE, KYOICHI A	PHARMASSET, INC.	2000	\$100,000
DESIGN OF EBVTK SUBSTRATES TO ERADICATE EBV+ TUMORS	FINGEROTH, JOYCE DIANE	PHARMASSET, INC.	2001	\$100,000
ANTIVIRALS AGAINST HBV	OTTO, MICHAEL J	PHARMASSET, INC.	2001	\$147,584
NOVEL BENZAMIDE RIBOSIDE ANALOGUES AS ANTICANCER AGENTS	PANKIEWICZ, KRZYSZTOF W	PHARMASSET, INC.	2001	\$249,998
AZIDE TECHNOLOGY FOR DRUG DEVELOPMENT	WATANABE, KYOICHI A	PHARMASSET, INC.	2001	\$132,879
MODIFIED NUCLEOSIDES FOR HEPATITIS C VIRUS	STUYVER, LIEVEN J	PHARMASSET, INC.	2002	\$162,200
ANTI-POXVIRUS NUCLEOSIDES:SYNTHESIS AND EVALUATION	WATANABE, KYOICHI A	PHARMASSET, INC.	2002	\$214,155
ENHANCEMENT OF 5-FLUOROURACIL CHEMOTHERAPEUTIC EFFICACY	EL KOUNI, MAHMOUD H	PHARMASSET, INC.	2002	\$176,852
DIOXOLANE NUCLEOSIDES AS ANTIVIRAL AGENTS	DU, JINFA	PHARMASSET, INC.	2003	\$175,260
NOVEL CLASS OF COMPOUNDS FOR TREATMENT OF HCV INFECTIONS	PANKIEWICZ, KRZYSZTOF W	PHARMASSET, INC.	2003	\$175,000
NOVEL AGENTS AGAINST WEST NILE VIRUS INFECTIONS	PANKIEWICZ, KRZYSZTOF W	PHARMASSET, INC.	2003	\$100,000
2'-AND/OR 4'-C-MODIFIED NUCLEOSIDES AS ANTI-HCV AGENTS	DU, JINFA	PHARMASSET, INC.	2004	\$189,277
2'-AND/OR 4'-C-MODIFIED NUCLEOSIDES AS ANTI-HCV AGENTS	DU, JINFA	PHARMASSET, INC.	2005	\$194,954
				\$2,460,170
TOTAL				o
Hepatitis related				\$1,011,015

Appendix C: Organization-level Finances of Pharmasset and Gilead Sciences

This appendix covers the financial metrics of Pharmasset and Gilead Sciences. For Pharmasset, I cover the major sources of financing, since it was a start-up biotechnology with no approved products or sources of sales revenue. For Gilead Sciences, I provide its main financial metrics in the five years (2007-2011) before its acquisition of Pharmasset at the end of 2011 as well as the five years after its acquisition of Pharmasset (2012-2016) which includes the launch of its hepatitis C medicines.

Pharmasset

Financing sources (all figures in millions)

Period	Financing source	Amount
2000-2005	SBIR	\$2.46
1999-2004	Venture Capital	\$53.81
2004-2010	Roche partnership	\$44.50
2007	Initial public offering	\$45.00
2008-2011	Follow-on equity financing	\$345.87
	TOTAL FINANCING, 2011-2011	\$491.66
	TOTAL OPERATING LOSS, 2001-2011	-\$313.9

Sources: Pharmasset SEC filings, S&P Capital database

Revenues, R&D Costs, Total Expenses, and Operating Loss: 2001-2011 (all figures in thousands)

	2001	2002	2003	2004	2005	2006	2007
Revenues	\$3,683	\$3,692	\$1,047	\$2,753	\$3,719	\$5,425	\$22,010
R&D	\$4,264	\$5,751	\$4,809	\$5,317	\$10,468	\$10,498	\$20,319
Total Expenses	\$5,470	\$7,072	\$6,570	\$8,215	\$18,564	\$18,410	\$29,530
Operating Loss	-\$1,787	-\$3,380	-\$5,523	-\$5,462	-\$14,845	-\$12,985	-\$7,520

	2008	2009	2010	2011*	TOTALS
Revenues	\$1,857	\$13,293	\$1,020	\$897	\$59,396
R&D	\$42,996	\$52,552	\$48,261	\$75,850	\$281,085
Total Expenses	\$56,285	\$65,917	\$64,719	\$92,501	\$373,253
Operating Loss	-\$54,428	-\$52,624	-\$63,699	-\$91,604	-\$313,857

*Pharmasset acquired by Gilead Sciences, November 2011

Gilead Sciences (all figures in millions)

2007 -2011 (before sofosbuvir)

					<i>Pharmasset acquisition</i>
	2007	2008	2009	2010	2011
Revenue	\$4,230	\$5,336	\$7,011	\$7,949	\$8,385
Research and development	\$591	\$722	\$914	\$1,073	\$1,229
Taxes	\$635	\$702	\$876	\$1,024	\$862
Buybacks and dividends	\$487	\$1,970	\$998	\$4,002	\$2,380
Cash and cash equivalents	\$2,722	\$3,239	\$3,905	\$5,318	\$9,900

2012-2016 (accounting for sofosbuvir launch)

		<i>sofosbuvir launch in December 2013</i>			
	2012	2013	2014	2015	2016
Revenue	\$9,702	\$11,202	\$24,890	\$32,151	\$29,953
Research and development	\$1,652	\$2,120	\$2,854	\$3,014	\$5,098
Taxes	\$1,038	\$1,151	\$2,797	\$3,553	\$3,609
Buybacks and dividends	\$313	\$6,010	\$5,349	\$11,876	\$13,456
Cash and cash equivalents	\$2,582	\$2,571	\$11,726	\$26,208	\$32,280

Sources: Gilead 2016, 2012, 2009 SEC filings.

Appendix D: Health economics analyzes of *sofosbuvir*'s value

Health economic studies analyzed the value of *sofosbuvir*-based medicines from two perspectives: (1) 'cost-effectiveness' value, in which the costs and benefits of new *sofosbuvir*-based medicines are compared versus the existing standard of care, as well as (2) 'public health prevention value', in which the averted costs of downstream medical care are calculated. In this appendix, I provide a technical summary of the methodologies used in these health economics studies of 'value' (D1 – D3), and list the main studies in D4. Each of these studies affirmed that *sofosbuvir*-based medicines were priced on a 'value' basis within the conventions of health economics modeling.

D1. 'Cost-effectiveness value' (See Clement (2009) and Groose (2014) for more.)

Cost-effectiveness is central to the health technology assessment (HTA) process undertaken by most European governments, and is increasingly being assessed by different public and private payers in the US.

- 1) Two different courses of action are defined for comparison: one of which may be called reference R (for example, a prior standard of care such as interferon, as was the case in hepatitis C) and the other proposed as alternative A (ex. *sofosbuvir*-based regimens).
- 2) The next step is quantitatively identifying and measuring the costs and benefits of each of the two courses of actions. The costs are monetized (based on the price of the therapy) whereas the benefits are measured using quality adjusted life years (QALYs) that collapse multi-dimensional health outcome changes into a single metric of health. See D3 below for a brief explainer on the QALY.
- 3) A cost-effectiveness ratio is calculated, by taking the differences in the costs (numerator) over the differences in the benefits (denominator). This calculation leads to a 'cost per QALY' ratio, indicating the amount of money required to realize an additional quality adjusted life year.
- 4) In the case of evaluating new medicines, this ratio is then compared against a "value threshold", or the amount of money that a given health system is willing to pay in exchange for a QALY gain. This value threshold is variable from health system to health system: in the NHS, this figure is between 30-40K USD per QALY gain, whereas US health economists use a figure of \$100,000-\$150,000 USD per QALY gain. If the cost-effectiveness ratio of a new drug falls under the value threshold, the price is deemed to be a 'value-based price'. The use and acceptance of these thresholds enables investors to anticipate that health systems will pay higher prices in the future for an improvement in health outcomes.

D2. 'Public health prevention value' (See Van Nuys (2015) and Castenada (2017) for more.)

A second valuation strategy is to calculate the total value gained from early treatment in terms of savings from averted medical expenses (and in some studies, value of additional QALYs accrued to society). This is done in several steps:

- 1) Define the R reference (standard of care) and A (alternative new potential standard of care).
- 2) Build a model of a population under the two scenarios.
- 3) Model the population's health status (morbidity and mortality) across a given time frame (ex. 10 years, 30 years, 50 years) under treatments R and A.
- 4) Calculate all medical costs for this sample population (could be all of the US, for example) under B and A.
- 5) Calculate the difference in medical costs under treatments B and A to see if and how much treatment A yields averted medical costs, thereby saving money for the health system.
- 6) In some studies: aggregate the total QALYs gained in a population in a given time frame based on using treatment A versus treatment R, and impute a value for these QALY gains based on

the economic value a health system attributes to each additional quality adjusted life year (similar to the value threshold described in section D1 earlier).

D3. A short QALY explainer

1. The quality-adjusted life year (QALY) is used most frequently with health technology assessment for medications. Under the QALY approach, life years lived in less than perfect health are converted into what the representative individual would consider the equivalent number of years in perfect health.
2. The noted health economist Uwe Reinhard explains how it works: “For example, if a person said he or she would be indifferent between living 20 more years in a particular lower health status described to him or her and only 16 more years in perfect health, then each of the 20 years in less than perfect health would be considered by that person the equivalent of $16/20 = 4/5 = .8$ of a health year, or .8 QALYs.”
3. These assessments are gathered via a number of games and interviews performed with patients, such as visual analogue scales, standard gamble, and time trade-off adjustors. For more on these methods, please refer to Reinhard 1998.

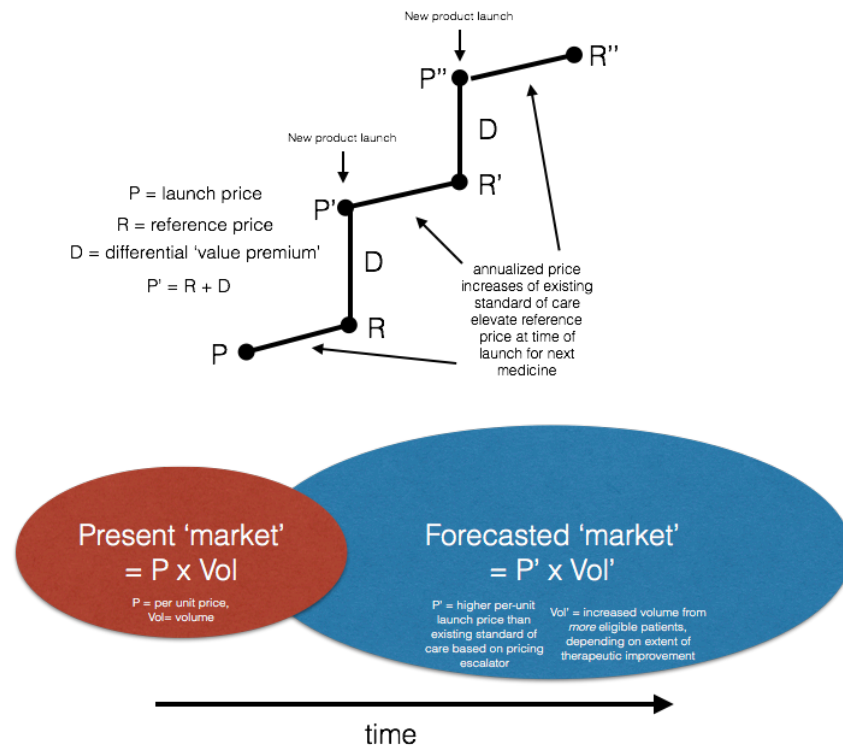
See Weinstein (2009) for more.

D4. Listing of health economics studies analyzing value of sofosbuvir-based medicines

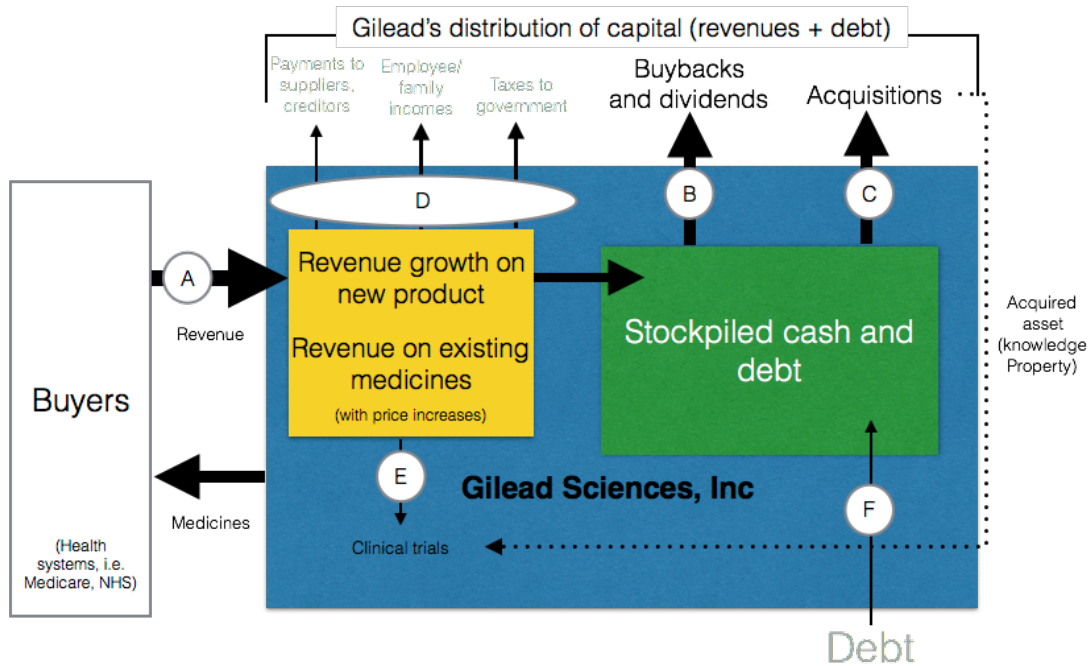
1. Chhatwal J, Kanwal F, Roberts MS, Dunn MA. Cost-Effectiveness and Budget Impact of Hepatitis C Virus Treatment With Sofosbuvir and Ledipasvir in the United States. *Annals of Internal Medicine*. 2015 Mar 17;162(6):397.
2. Tice JA, Chahal HS, Ollendorf DA. Comparative Clinical Effectiveness and Value of Novel Interferon-Free Combination Therapy for Hepatitis C Genotype 1. *JAMA Intern Med*. 2015;175(9):1559
3. Najafzadeh, M., Andersson, K., Shrank, W. H., Krumme, A. A., Matlin, O. S., Brennan, T., et al. (2015). Cost-Effectiveness of Novel Regimens for the Treatment of Hepatitis C Virus. *Annals of Internal Medicine*, 162(6), 407. <http://doi.org/10.7326/M14-1152>
4. Rein DB, Wittenborn JS, Smith BD, Liffmann DK, Ward JW. The Cost-effectiveness, Health Benefits, and Financial Costs of New Antiviral Treatments for Hepatitis C Virus. *Clin Infect Dis*. 2015 Jun 25;61(2):157–68.
5. Leidner AJ, Chesson HW, Xu F, Ward JW, Spradling PR, Holmberg SD. Cost-effectiveness of hepatitis C treatment for patients in early stages of liver disease. *Hepatology*. 2015 Jun;61(6):1860–9.
6. Van Nuys, K., Brookmeyer, R., Chou, J. W., Dreyfus, D., Dieterich, D., & Goldman, D. P. (2015). Broad Hepatitis C Treatment Scenarios Return Substantial Health Gains, But Capacity Is A Concern. *Health Affairs*, 34(10), 1666–1674. <http://doi.org/10.1377/hlthaff.2014.1193> *Gilead's executive vice president, Gregg Alton, serves on the board of the institute that led this study.*
7. Chahal HS, Marseille EA, Tice JA, Pearson SD, Ollendorf DA, Fox RK, et al. Cost-effectiveness of Early Treatment of Hepatitis C Virus Genotype 1 by Stage of Liver Fibrosis in a US Treatment-Naive Population. *JAMA Intern Med*. American Medical Association; 2016 Jan;176(1):65–73.
8. Younossi, Z. M., Park, H., Dieterich, D., Saab, S., Ahmed, A., & Gordon, S. C. (2016). The value of cure associated with treating treatment-naïve chronic hepatitis C genotype 1: Are the new all-oral regimens good value to society? *Liver International*. <http://doi.org/10.1111/liv.13298>

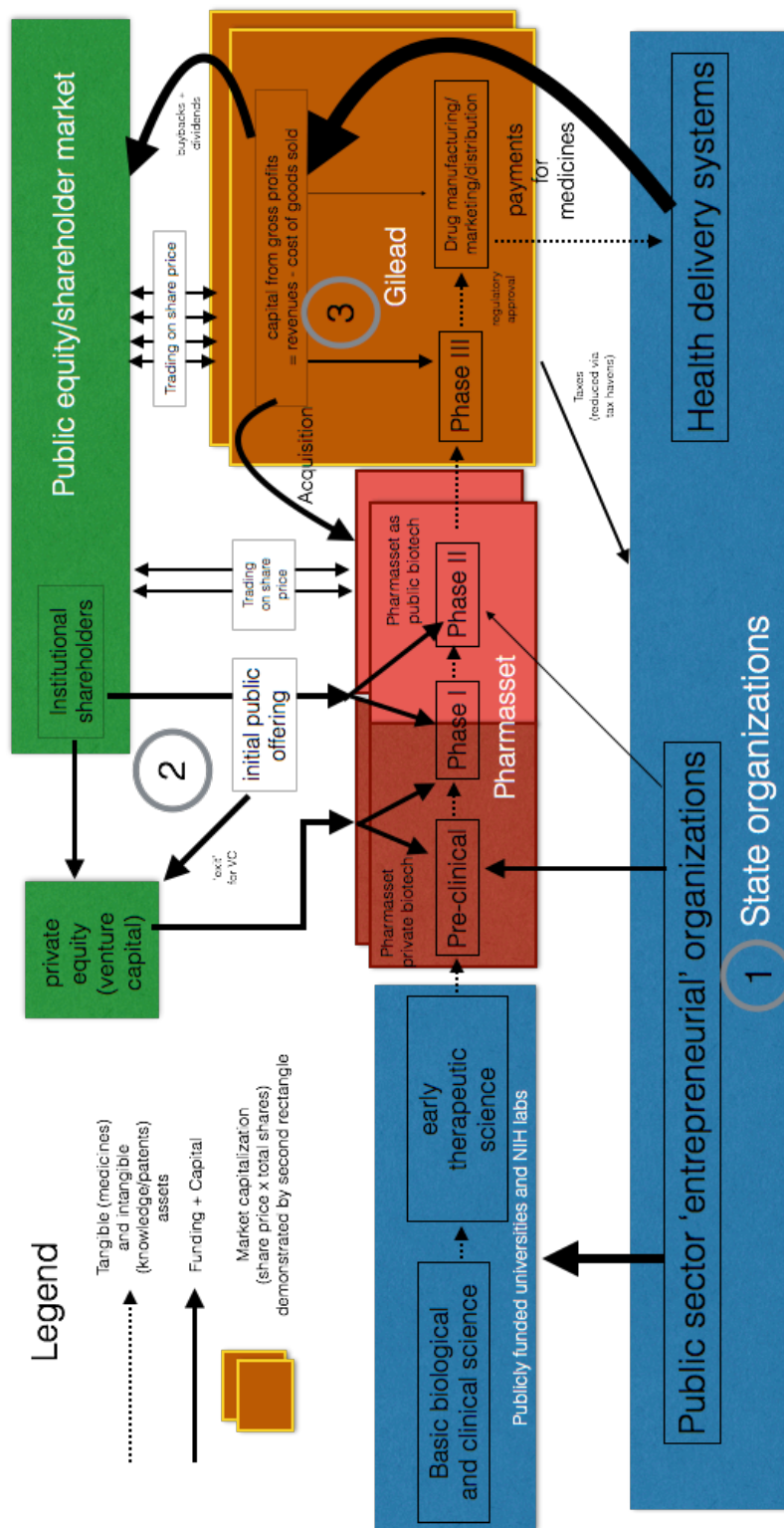
Appendix E: Key Diagrams Depicting Innovation Process

Pricing escalator (from chapter 4, section 4.1)



Gilead's capital allocation strategy (from chapter 5, section 5.3)





- Three core takeaways**
- 1 State provided (a) long-term funding across multiple stages of research that supported a curative direction for innovation as well as (b) payment for patent-protected prices of new medicines.
 - 2 Venture capital and the IPO mobilized capital for Pharmasset, with portion used for R&D; risk was mitigated by existence of liquid, downstream trading market which allowed for exits. Using share price as the core metric, capitalists in public and private equity markets traded in large part on future earnings potential from hepatitis C market valuation forecasts (based on anticipating increasing drug prices for better outcomes).
 - 3 An established publicly traded company, Gilead used its accumulated capital, derived from revenues for patent protected pricing, primarily on acquisitions (in this case Pharmasset) and shareholder dispersals (buybacks and dividends).

